STUDY OF RISK FACTORS IN PATIENT WITH ADVANCED FIBROSIS IN NON ALCOHOLIC FATTY LIVER DISEASE WITH MILD ELEVATION OF TRANSAMINASES

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Dedicated

to

my Family

&

Teachers

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Dr. Gautam Bedi

ABBREVIATIONS

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
FIB-4	Fibrosis score
HCC	Hepatocellular carcinoma
HDL	High density lipoprotein
HFF	Hepatic fat fraction
HOMA-IR	Homeostasis model assessment – estimated insulin resistance
LDL	Low density lipoprotein
MS	Metabolic syndrome
NAFLD	Non alcoholic fatty liver disease
NASH	Non alcoholic steatohepatitis
PCOS	Polycystic ovarian syndrome
PNPLA3	Patatin-like phospholipase domain-containing protein 3
TC	Total cholesterol
TG	Triglycerides
TPN	Total parenteral nutrition
VLDL	Very low density lipoprotein

ABSTRACT

Introduction - Nonalcoholic fatty liver (NAFLD) is a global health problem. Most important predictor of adverse outcome in NAFLD is fibrosis. Advance fibrosis in NAFLD is serious condition which can lead on to hepatocellular carcinoma and various complications of cirrhosis. The histological spectrum of NAFLD range from simple steatosis to steatohepatitis and fibrosis. Various risk factors such as obesity, metabolic syndrome and diabetes have been implicated with NAFLD and each of them has different prevalence.

Aim of Study: To analyze the risk factors in patient with advanced fibrosis with nonalcoholic fatty liver disease, who have mild elevation of transaminases levels.

Materials & methods: In our study 90 patients with advanced fibrosis in NAFLD were taken and risk factors were observed in Department of Medicine and Department of Gastroenterology at Dayanand medical college and hospital, Ludhiana from March 2021 to Feb 2022.

Results: We observed the risk factors of advanced fibrosis in NAFLD, out of all patients of advanced fibrosis seen 78.9% patient had diabetes mellitus with mean HbA1C level of 8.94% with standard deviation of 1.60 and most patients were on oral hypoglycemic agents. In ours study 85.6% patient had metabolic syndrome with p value of <0.05 and 14.4 % patient didn't had metabolic syndrome. Patients with advanced fibrosis had a mean age of 63.01 with standard deviation of 11.11 years. In our study 54.4% were male and 45.6% were females. In our study mean platelet count was 96755.56 ± 43945.40, mean AST/ALT ratio was 0.95± 0.2. In our study 77.5% males had a waist circumference more than the cut off value and all of the females who had advanced fibrosis with NAFLD had a waist circumference more than cut off value for metabolic complications. In our study mean HOMA-IR was 3.53 ± 1.14 which indicated most of the patient who had advanced fibrosis in NAFLD had insulin resistance. In our study we also saw that patients who had metabolic syndrome had a mean HOMA IR of 3.84 ± 0.89 and patients who didn't had metabolic syndrome had a HOMA-IR of 1.72 ± 0.68 with a positive statistical association with p value of <0.05. In patients with metabolic syndrome mean BMI was 28.02 ± 3.19 kg/m^2 where as in patient who didn't had metabolic syndrome had a mean BMI of 23.7 ± 2.03 kg/m^2 with a positive statistical association with p value of <0.05.

Conclusion: In our study we conclude that patients with metabolic syndrome, diabetes mellitus, dyslipidemias, old age, obesity should be screened for advanced fibrosis in NAFLD. Patients with high levels of HOMA-IR, LDL, HDL, total cholesterol should also be screened for advanced fibrosis with NAFLD. Patients with high HOMA-IR have high risk for metabolic syndrome.

Keywords: Nafld, Fibrosis, Ast, Alt, Obesity, Metabolic syndrome, Diabetes Mellitus, Transient Elastography

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INTRODUCTION

The phrase "non-alcoholic fatty liver disease" (NAFLD) refers to a spectrum of conditions ranging from the harmless accumulation of fat in the liver to the more serious steatosis, hepatitis, fibrosis, cirrhosis, and even hepatocellular carcinoma (HCC) that can develop later on.[1] The histological spectrum of NAFLD is broad, ranging from simple steatosis to steatohepatitis (NASH). The presence of steatosis is estimated by counting the number of fat droplets per unit of hepatocytes.[2]

Due to its potential to proceed to cirrhosis and liver failure, nonalcoholic fatty liver disease is gaining recognition as a major cause of liver-related morbidity and mortality. Fat accumulation in the liver of a non-alcoholic person is called non-alcoholic fatty liver disease (NAFLD), and it can lead to cirrhosis and liver failure. Falck-Ytter and colleagues[2] conducted the research in 2001.

Twenty percent of adult Americans live with non-alcoholic fatty liver disease (NAFLD). Ten percent to twenty four percent of the population have it globally. The prevalence increases to 57-74% among the overweight and 25-75% among the obese who are diabetic. Therefore, behind alcoholism and hepatitis C, NASH is thought to be the another leading cause of liver disease. Simple steatosis, non-alcoholic steatohepatitis, hepatic fibrosis, cirrhosis, and liver failure are all more likely to occur in patients with Diabetes mellitus. In addition, the death rate is three times higher in those with diabetes and NAFLD than in those with NAFLD who do not have diabetes.

Both non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) are included in the umbrella term NAFLD.[1] Liver steatosis, affecting more than 5% of parenchyma, without hepatocyte damage, is diagnostic of nonalcoholic fatty liver disease (NAFL).[3] The histological definition of NASH is a necroinflammatory process in which steatosis

causes liver cell injury.[3] While the whole course of NAFLD's natural history is still being pieced together, the published data point to a high risk of cirrhosis and HCC.[4] Although it is still being researched, preliminary data suggests that there may be a distinct progression from NAFL to NASH.[1] Several epidemiological studies have attempted to calculate an accurate worldwide incidence of NAFL/NASH; however, because of extensive differences in study parameters and accessible testing, no clear and trustworthy occurrence rate is currently available[1]. However, some have hypothesised that the prevalence of NAFLD is closer to 20%-30% in Western countries and 5%-18% in Asia[1]. Given the current trends in dietary irresponsibility and the preponderance of a sedentary lifestyle, it is not surprising that the prevalence of NAFLD is increasing with each passing year around the world[1]. Furthermore, NAFLD incidence has increased in tandem with diabetes and metabolic syndrome[4]. Researchers in the United States found that the prevalence of NAFLD was 10% more in obese people than in slimmer people[5]. NAFLD is expected to overtake cirrhosis as the largest cause of liver-related morbidity and mortality and the most common reason for liver transplantation during the next two decades[4]. Nonalcoholic fatty liver disease is the second leading cause of liver transplant waiting lists[6]. In addition to putting a burden on healthcare providers and their facilities, NAFLD is linked to a higher mortality rate (34%-69%) than the general population in the following 15 years[6]. Cardiovascular disease is the leading cause of death in those with NAFLD, with liver-related deaths accounting for only 5% of all deaths in this population[6,7].

Mild steatosis, non-alcoholic steatohepatitis (NASH), increasing fibrosis, cirrhosis, and eventually hepatocellular carcinoma are all parts of the range of clinical and histological manifestations that make up non-alcoholic fatty liver disease (NAFLD)[7].Hepatic steatosis[7,8,9] and advanced liver disease (NAFLD) are strongly associated with metabolic syndrome[10,9]. It is common practise to do a liver biopsy on individuals with

NAFLD who have elevated serum alanine aminotransferase (ALT) levels to identify if they have developed nonalcoholic steatohepatitis (NASH) and advanced fibrosis[9]. Previous research has linked high ALT levels to nonalcoholic steatohepatitis and progressive fibrosis[11]. However, patients with normal ALT levels may develop NASH and severe fibrosis[7,9]. Whether or not NAFLD patients with normal ALT levels should get a liver biopsy to confirm NASH or advanced fibrosis is a clinically relevant question that arises from the lack of a systematic link between ALT level and advanced form of NAFLD[9]. Consequently, a level that may check for advanced liver disease, such as NASH and advanced fibrosis, without necessarily requiring a liver biopsy, requires predictive ALT levels.

The noninvasive fatty liver disease fibrosis score (NAFLD fibrosis score) classifies patients into one of three subgroups based on their scores across six indicators associated with liver fibrosis.F0-F2= <-1.455, Intermediate= -1.455-0.675,F3- F4=>0.675.Damage to the hepatocytes (ballooning, apoptosis/necrosis, Mallory's hyaline, big mitochondria), inflammation, and fibrosis (perisinusoidal, pericellular) are all hallmarks of steatohepatitis[12,13]. There is some disagreement over how much alcohol one should drink to be able to tell the difference between alcoholic fatty liver and nonalcoholic fatty liver disease. To define NAFLD, many centres agree that men can safely consume up to two standard drinks per day (140 g ethanol/week), and women can safely consume up to one standard drink per day (70 g ethanol/week)[14].

Depending on the cause, NAFLD can be classified as either primary or secondary. Insulin resistance and metabolic syndrome have been linked to primary NAFLD. Total parenteral nutrition (TPN), acute starvation (AS), abdominal surgery (e.g., extensive small bowel resection, biliopancreatic diversion, and jejunal bypass), and the use of many medicines have also been linked to nonalcoholic fatty liver disease (NAFLD) (e.g. amiodarone, tamoxifen, glucocorticoids, synthetic estrogens, diltiazem, aspirin,

methotrexate, highly active antiretroviral therapy). Hypobetalipoproteinemia, lipodystrophy, hypopituitarism, hypothalamic obesity, Weber-Christian syndrome, acute fatty liver of pregnancy, Reyes syndrome, and Mauriac syndrome are all linked to it[15,16]. Studies suggest that women with polycystic ovarian syndrome may have a higher prevalence of NAFLD, and that occupational exposure to organic solvents may play a role in the development of NAFLD[17,18].

Very few studies for risk factor of advance fibrosis in NAFLD are known in north indian, so this study, evaluate the risk factors for severe fibrosis in patients with nonalcoholic fatty liver disease with mildly raised transaminases.

AIMS & OBJECTIVES

To analyse the risk factors in patient with non alcoholic fatty liver disease with advanced fibrosis, who have mild elevation in transaminases.

REVIEW OF LITERATURE

The range of liver disease that includes steatosis, steatohepatitis that can lead to liver cirrhosis, and even hepatocellular cancer is summed up under the umbrella term of nonalcoholic fatty liver disease (NAFLD). Other researchers have replicated these findings[2,19]. Ludwig et al. (1980)[20] used nonalcoholic steatohepatitis (NASH) to describe liver damage that resembled alcoholic hepatitis histologically but was seen in overweight, diabetic women who denied ever drinking alcohol. Researchers have calculated that 10%-24% of the population has NAFLD, while 1%-5% has NASH. The incidence and severity of nonalcoholic fatty liver disease (NAFLD) are both significantly associated with body mass index (BMI). In the obese (57.5–74%) and the severely obese (90%) NAFLD prevalence dramatically increased. Multiple studies[21,22] support this theory. Approximately 9-32% of the Indian population suffers from non-alcoholic fatty liver disease[33].

Elevated liver enzymes are often an accidental finding in patients with NAFLD, and most have no symptoms. The liver enzymes alanine amino transferase and aspartate amino transferase are typically high in NAFLD; however, there is no consistent correlation between these elevated levels and hepatic damage, inflammation, or cirrhosis.

Natural History Of NAFLD:

NAFLD has a prevalence of about 25% worldwide, with rates as low as 13% in Africa, 23% in Europe, and 32% in the Middle East[24]. Geographical variation is a reflection of the known differences in disease incidence and severity between different ethnic groups, most notably a protective effect of black ethnicity and conversely higher rates of NASH in Hispanic groups[25], perhaps in part due to higher frequency of genetic risk variants (eg rs738409 in PNPLA3) associated with NAFLD[26]. NAFLD is closely linked to other chronic diseases, such as type 2 diabetes (23%), central

obesity (51%), dyslipidaemia (69%), and metabolic syndrome (43%). Rising rates of obesity have contributed to a corresponding increase in the disease burden, which has gone from 15% in 2005 to 25% in 2010[24].

Histological characteristics of NASH are less predictive of poor outcomes in NAFLD than fibrosis[27].Even in the earliest stages of fibrosis, there is an increase in all-cause mortality, mortality which increases linearly with further fibrosis progression. Mortality rates from liver disease with bridging fibrosis (F3) and cirrhosis (F4) are 7.92 (per 1000 person-years follow-up against stage 0 fibrosis) and 23.3 (per 1000 person-years follow-up vs stage 0 fibrosis), respectively[28]. Fibrosis progresses very slowly in NAFLD, but it advances much more quickly in patients with NASH (7 years per fibrosis stage) than in those without NASH (14 years), indicating the significance of NASH in the progression of fibrosis[29]. Ageing, increased body mass index, and diabetes are potential precursors to disease progression[30].

Heart disease accounts for about 40% of deaths in those with NAFLD. Studies have shown that NAFLD may independently increase the risk of heart disease[31], though this has not yet been incorporated into cardiovascular risk-assessment tools.

Only a small percentage of people with NAFLD will progress to cirrhosis and ultimately die, and even fewer will develop hepatocellular carcinoma (HCC)[24]. However, the number of people requiring a liver transplant due to NAFLD is rising. From 2004-2013, the number of transplant-eligible patients with NASH in the United States increased by 170 percent, according to data compiled by Wong et al. (2015)[32]. Therefore, it is expected that NASH will overtake alcoholism as the top reason for liver transplantation in the United States within the next decade[33]. Further research is needed in this area, as some studies have shown that NAFLD may predispose patients to HCC without cirrhosis[34].

Risk Factors Of NAFLD

- **Metabolic syndrome and type 2 diabetes mellitus**

Type II diabetes and cardiovascular disease are more likely in people with metabolic syndrome, a cluster of risk factors for these conditions[35]. To meet the current diagnostic criteria, at least three of the following five conditions must be present: Hyperglycemia (defined as fasting glucose 100 g/dL or greater), an increased waist circumference (as defined by population-specific data), and hypertension (defined as systolic blood pressure 130 mmHg or greater or diastolic blood pressure 85 mmHg or greater) are all risk factors for cardiovascular disease[35]. Metabolic syndrome, which includes NAFLD, is on the rise, and its prevalence is expanding alongside it. It has been shown that more criteria for metabolic syndrome are associated with a higher risk of NAFLD[3]. T2DM patients have 80% greater liver fat contents than age-, sex-, and weight-matched non-diabetic patients[35]. Even if the prevalence of NAFLD in T2DM patients is higher than reported, it has been demonstrated that T2DM patients with NAFLD can have normal liver function tests[35]. Patients with type 2 diabetes mellitus have a two- to four-fold greater risk of problems related to fatty liver disease.[35,36].

- **Ethnic differences**

The rate at which NAFLD develops is greatest in Hispanic patients[37]. Also, NAFLD in the Asian population has been increasing, and interestingly, it can be seen in those with a normal body mass index[37]. In a United States-based study, the investigators found a lower degree of steatosis in African Americans compared to whites. Also, they showed a higher degree of NAFLD findings in Asians and Hispanics[38]. The Hispanic population also has been shown to have a higher occurrence of steatohepatitis and cirrhosis, while those who are African American enjoy a decreased chance of developing liver failure[39]. With further genetic investigation by genome-wide association, it was noted that Hispanics had a twofold higher liver fat

content if they possessed the homozygous PNPLA3 allele (patatin-like phospholipase domain-containing protein 3 rs738409)[39]. The PNPLA3 gene family has been shown to affect lipid metabolism, and patients who harbour this polymorphism were found to have increased hepatic fat content, triglyceride stores, and inflammation[37]. The mutation of the PNPLA3 rs738409 gene (encoding I148M) has revealed more severe histologic features of NAFLD in those carrying the mutation[37]. More information on the genetic basis for NAFLD can be found under the "genetics" heading.

- **Gender and age**

Unfortunately, the role of gender in the development of NAFLD has been met with differing conclusions. Various studies suggest a higher prevalence in males, while others proposed the opposite[1]. However, according to Lonardo et al., (2015)[35] epidemiological review, NAFLD is more common in men and has been shown to increase in those who are younger to middle-aged, with a decline noted after the age of 50 years. In contrast, NAFLD spares those women who are pre-menopausal and then a rise in incidence is noted after the age of 50 with a peak at 60-69 years. The preponderance of the evidence suggest that NASH is histologically more severe in women when compared to men[35]. It has been reported that the prevalence of NAFLD increases with age (20% in people younger than 20) to greater than 40% in those whoare older than 60 years of age[40]. Also, the incidence of NASH and cirrhosis increase in those patients who are 50 years of age or greater compared with younger age groups[1]. Notably, it has been suggested that NAFLD begins in utero based on several magnetic resonance spectroscopy studies showing steatosis in infants born to motherswith gestational diabetes (GD)[41]. In a study using hepatic fat fraction (HFF), performed at 1-3 wk of age in neonates born to normal mothers compared to those with gestational diabetes, neonates born to obese mothers with GD had a mean HFF that was 68% higher than those born to non obese mothers[42]. In another study by Patel et al.,

(2015)[43], 33 stillborn babies of diabetic mothers were compared with 48 stillborn babies of mothers without diabetes, and there was a markedly increased rate of hepatic steatosis in neonates born to mothers with diabetes (79%) vs controls (17%). A study with 191 Italian children with biopsy-confirmed NAFLD showed hepatic steatosis, inflammation, hepatocyte ballooning, and fibrosis were worse in those not breastfed childrenthan those who were[44]. Similar to what has been observed in adults, obesity is a considerable risk factor for developing NAFLD in children[45]. According to the Child and Adolescent Liver Epidemiology Study, about one-third of obese children have NAFLD[46]. With that being said, a fatty liver is the most common liver abnormality found in children aged 2-19 years[46]. Again like that seen in adulthood, pediatric NAFLD and cardiovascular disease are associated with higher levels of total cholesterol, LDL, triglycerides, and systolic blood pressure reported[45]. Currently, the incidence of HCC in the pediatric population with NALFD is not known andis thought to be rare[41]. Only one case report of HCC with concurrent NAFLD in a 7-year-old boy has been reported[47]. Longitudinal outcomes are sparse for pediatric patients with NAFLD; however, what is known is that children can present with cirrhosis at diagnosis and may progress from NASH to cirrhosis[48].

- **Diet, smoking and life style**

The development of NAFLD has been linked to a high-fat diet, which has been considered a separate risk factor[39]. Energy restriction and adjustment of dietary macronutrients, such as restriction of carbohydrates, fat, or enrichment with monounsaturated fatty acids, have been proven to ameliorate metabolic syndrome[49]. A higher risk of metabolic syndrome and NAFLD is related to a Western-style diet, characterised by an abundance of red meat, refined carbohydrates, pastries, and sugar-laden beverages[39]. Cigarette smoking was identified as a significant contributor to the development of NAFLD in a retrospective investigation involving

2029 people.[50] Insulin resistance is more likely to occur in people who smoke cigarettes[51,52].

Furthermore, both passive and active smoking are significant independent predictors of metabolic syndrome in a study of American adolescents[53]. Both nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) have been linked to lifestyle factors like inactivity and lack of fitness, and NAFLD is worsened by less exercise[39]. According to the EASL-EASD-EASO Clinical practise guidelines for managing NAFLD, a thorough NAFLD screening exam should include a recommendation for assessing physical activity habits[54]. Diet and exercise are incorporated into the treatment plan for NAFLD to help with obesity and insulin resistance. Multiple studies have looked at the impact of a healthy diet on NAFLD biologic markers, and they all point to the benefits of slow, steady weight loss. Serum liver enzymes, hepatic fatty infiltration, hepatic inflammation, and fibrosis have all been demonstrated to improve with steady weight loss through diet, with or without exercise[55]. In addition, exercise has a demonstrable positive effect on hepatic fatty infiltration. This effect persists even in the absence of significant weight loss and at exercise intensities well below those suggested for the therapy of obesity[56]. A systematic analysis found that NAFLD patients with low cardiorespiratory fitness and who cannot endure severe aerobic exercise were benefited from resistance exercise (as opposed to the therapeutic advantages of aerobic exercises like running)[57].

- **Polycystic ovarian syndrome**

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder of reproductive-aged women and is characterized by obesity and insulin resistance[58]. Hence, women with PCOS have high risk of developing T2DM[58]. In a study that evaluated 600 women with PCOS and 125 body mass index (BMI)-matched healthy control women, the prevalence of NAFLD was higher in those with PCOS[58]. Insulin resistance and obesity,

are known to contribute to the development of NAFLD. Women with PCOShave hyperandrogenemia, and insulin resistance worsens the hyperandrogenemia by increasing ovarian androgen synthesis and decreasing liver SHBG production, which results in elevated circulating levels of free androgens[58]. The hyperandrogenemia further leads to more prominent insulin resistance in patients with PCOS, which endangers these patients to develop NAFLD[58]. Numerous other investigations into the association of PCOS and NAFLD have been performed, and similar results were obtained[59,60].

- **Obstructive sleep apnea**

Obstructive sleep apnea (OSA) is characterized by complete or partial airway obstruction caused by pharyngeal collapse during sleep[61]. A strong association between OSA and diabetes mellitus, metabolic syndrome, and cardiovascular disease has started to appear in the last few years[61]. In the general population, obstructive sleep apnea has a prevalence of around 4%, with that number increasesto 35%-45% in obese individuals[39]. In a study performed by Tanné et al., (2005)[62], patients with severe OSA were found to be more insulin resistant. Therewas higher percentage of steatosis and increased necrosis and fibrosis scores (on liver biopsy)when compared to those patients without OSA and a similar BMI. The pathogenic mechanisms involved in this association is believed to be due to the alteration of gas exchange (repetitive hypoxemic and hypercapnic events), termed chronic intermittent hypoxia, which can lead to an increase in proinflammatory cytokines, endothelial dysfunction, oxidative stress, metabolic dysregulation, and finally resulting in insulin resistance[61]. Interestingly, OSA may be one of the elements promoting the evolution of NAFLD from steatosis to NASH[62]. Additionally, using animal models, OSA was shown to promote the digression of NAFLD to NASH.[39]Investigational evidence has suggested that chronic intermittent hypoxia may trigger liver injury, inflammation, and fibrogenesis, with several studies showing relationship between OSA and NASH[61,62,63].

- **Genetics**

Data from various studies suggest a heritable component of NAFLD and includes Familial aggregation, twin studies, and interethnic differences in susceptibility[64,65,66,25]. Whole exome sequencing studies done on obese Caucasian, with NAFLD revealed deleterious mutations in Bardet-Biedl syndrome 1 gene and the Melanocortin 3 receptor gene[67]. In 2008, the first genome-wide association study was published; it examined hepatic triacylglycerol (HTAG) accumulation and identified an association between increased HTAG and the PNPLA3 gene[26]. Subsequent work and various studies have confirmed this variant (PNPLA3 rs738409) in Japanese, Indian, and Chinese NAFLD patients[68,69,70]. In a meta-analysis of 24 studies with 9915 participants, Singal et al., (2014)[71]found that PNPLA3 was associated with increased risk of fibrosis. Additionally, among nine studies, totaling 2937 participants, the PNPLA3 was again linked with an increased risk for developing HCC in those patient who had cirrhosis[71]. A separate meta-analysis of 16 studies, revealed that the rs738409 GG genotype when compared to the CC genotype was linked to a 73% greater liver fat content and a 3.24-fold increased risk of more pronounced necroinflammatory scores and a 3.2-fold increased risk of developing fibrosis[72]. Xu et al., (2015)[73], by way of meta-analysis totalling 23 case-control studies (totaling 6071 NAFLD participants and 10366 controls) found the PNPLA3 rs738409 polymorphism to have a significant association with a high cross-ethnicity risk for NAFLD as well as NASH. Genome-wide association study performed on 236 non-Hispanic white women with NAFLD (324623 single nucleotide polymorphisms in total from 22 autosomal chromosomes) found the NAFLD activity score to be associated with the SNP rs2645424, the degree of fibrosis associated with SNP rs343062, lobular inflammation with SNPs rs1227756, rs6591182, and rs887304, increased levels of ALT was associated with SNPs rs2499604, rs6487679, rs1421201, and finally rs2710833[74]. Using exome-wide association, Kozlitina et al., (2014)[75] found three variants to be

associated with higher liver fat levels: Two in the PNPLA3 as mentioned above and one in the TM6SF2 gene, which likely is required for normal VLDL secretion. The variant frequency in the TM6SF2 gene was found to be highest in those of European, African-American, and Hispanic ancestry[67]. In a later study by Mahdessian et al (2014)[76]; the TM6SF2 gene was found to be a regulator of liver fat metabolism, influencing triglyceride secretion and hepatic lipid droplet content. About, 7 categories of genes have been associated with NAFLD. They are broken down as: (1) hepatic lipid export/oxidation in steatosis (PNPLA3, TM6SF2, NR1I2, PPAR-alpha, PEMT, MTTP, APOC3 and APOE); (2) glucose metabolism and insulin resistance (ENPP1/IRS1, GCKR, SLC2A1, GOAT, TCF7L2 and PPARG); (3) steatosis-hepatic lipid import or synthesis (SLC27A5, FADS1, and LPIN1); (4) steatohepatitis-oxidative stress (HFE, GCLC/GCLM, ABCC2 and SOD2); (5) steatohepatitis-endotoxin response (TLR4 and CD14); (6) cytokines (TNF and IL6); and (7) fibrosis (AGTR1 and KLF6)[77].

Previous studies have also explored the risk factors associated with Non-Alcoholic FattyLiver Disease in Indians.

In a study Singh et al., (2015)[78] identify the risk factors associated with NAFLD. Four hundred sixty-four consecutive NAFLD patients and 181 control patients were subjected to detailed questionnaires regarding their lifestyle and dietary risk factors. Anthropometric measurements were obtained and biochemical assays were done. A comparison of different variables was made between NAFLD patients and controls using principal component analysis (PCA). NAFLD patients had higher BMI [26.25 ± 3.80 vs 21.46 ± 3.08 kg/m2, P = 0.000], waist-hip ratio [0.96 ± 0.12 vs 0.90 ± 0.08, P = 0.000] and the waist-height ratio [0.57 ± 0.09 vs 0.50 ± 0.06, P = 0.000] compared to controls. Fasting blood sugar [101.88 ± 31.57 vs 90.87 ± 10.74 mg/dl] and triglyceride levels [196.16 ± 102.66 vs 133.20 ± 58.37 mg/dl] were significantly higher in NAFLD group. HOMA-IR was also

higher in NAFLD group [2.53 ± 2.57 vs 1.16 ± 0.58, P = 0.000]. Majority (90.2%) of NAFLD patients had sedentary life style. A family history of metabolic syndrome (MS) was positively correlated with NAFLD. Dietary risk factors associated with NAFLD were a non-vegetarian diet [35% vs 23%, P = 0.002], fried food [35% vs 9%, P = 0.000], spicy foods [51% vs 15%, P = 0.001] and tea [55% vs 39%, P = 0.001]. Diabetes, hypertension, snoring and OSA were common factors in NAFLD. On multivariate PCA, waist/height ratio and BMI were significantly higher in the NAFLD patients. The risk factors associated with NAFLD are a sedentary lifestyle, obesity, family history of MS, consumption of meat/fish, spicy foods, fried foods and tea. While,other risk factors are NAFLD included snoring and MS.

In their study, Gupta et al., (2020)[79] assessed the metabolic profiles and other associated risk factors of NAFLD. A total of 100 patients participated in the study. The mean age was 10.6 ± 2.6 years and the mean BMI-Z score was 2.6 ± 0.5. The prevalence of NAFLD was 62%. Alanine transaminase (ALT) was significantly elevated in all the children with NAFLD. Lipid levels and BMI Z-score were similar in both groups. The unadjusted odds ratio shows a statistically significant association of ALT (2.058 [1.11–1.01]) and waist circumference (1.089 [1.19–0.99]) with NAFLD. With an adjusted odds ratio only, ALT (1.12 [1.24–1.01]) was significantly associated with NAFLD. There is quite a high prevalence of nonalcoholic fatty liver in obese Indian patients. All patients with raised liver enzymes should undergo sonography to rule out NAFLD.

Kalra et al., (2022)[80] conducted a study to understand the prevalence of NAFLD along with the associated risk factors and their interaction with other comorbidities among people living with diabetes in Indian context. It is a retrospective, observational study based on data retrieved from electronic medical records (EMRs) of people living with diabetes from more than 250 individual diabetes centers located in more than 30 cities

across 14 states in India. Overall, 44.48% of people living with diabetes were found to have NAFLD. A significantly higher proportion of males (58.64%) had NAFLD compared to females (36.91%) ($p<0.001$). Nonalcoholic fatty liver disease prevalence was >50% in seven states. People living with diabetes, dyslipidemia, and hypertension had a significantly higher prevalence of NAFLD ($p<0.001$). Obesity (57.1%), dyslipidemia (59.1%), and hypertriglyceridemia (42.3%) had significantly higher risk of developing NAFLD among people living with diabetes. This study also highlighted high-risk categories for NAFLD with diabetes, like young, obese, hypertriglyceridemia, poor glycemic control, etc.

Amarapurkar et al., (2007)[81] conducted a study to estimate the prevalence of NAFLD in general population. Residents of two Railway colonies were evaluated on history, clinical examination, anthropometric measurements, biochemical tests and abdominal ultrasound. 1,168 participants were evaluated. The prevalence of NAFLD on ultrasound was 16.6%. Out of 730 subjects above the age of 20 years (341 male 384 female 389) mean age 39.08 ± 12.3 years, 4% had diabetes, 57% had central obesity. The prevalence of NAFLD based on the ultrasound above 20 years of age was 18.9%. In this study, NAFLD was more prevalent in male than female (24.6% vs 13.6%, $p < 0.001$). Risk factors that were associated with NAFLD were age of more than 40 years, male gender, central obesity, high BMI> 25, elevated fasting blood sugar, raised AST and ALT.

Overall, Non-alcoholic fatty liver disease (NAFLD) is a growing health concern characterized by the build-up of excess fat in the liver of individuals who drink little to no alcohol. Main risk factors for NAFLD are:[81,80,79]

- Obesity and excess weight
- Insulin resistance and type 2 diabetes
- High triglycerides and low HDL (good) cholesterol
- Metabolic syndrome

- Genetics: NAFLD can run in families, suggesting a genetic component to the disease.
- Rapid weight loss: Rapid weight loss, especially through bariatric surgery, can cause the liver to store more fat, increasing the risk of NAFLD.
- Ethnicity: NAFLD is more common in certain ethnic populations, including Hispanic, Middle Eastern, and Native American populations.
- Older Age
- Sedentary lifestyle

Etiopathogenesis Of NAFLD/NASH:

The pathogenesis of NASH is not completely understood. Various conditions associated with NAFLD include nutritional abnormalities, metabolic disorders, drugs, chemicals, and surgery.Initially, there is steatosis which, after a series of events, may progress to inflammation and fibrosis and finally to cirrhosis and end-stage liver disease[82,83,84] (Angulo, 2002; Chitturi& Farrell, 2001; Day & James, 1998). NASH may be considered a two-hit process, the first hit is the accumulation of fat and the second hit is a hepatocellular injury in the fatty liver[84].The first hit of steatosis genrally occurs because of the loss of balance between the fatty acid uptake, oxidation, esterification and export as very low-density lipoprotein (VLDL) from the hepatocytes. Insulin resistance is an important key factor[82,84,85], which leads to an increase in lipolysis and increased uptake of fatty acids by hepatocytes.

Hyperinsulinemia, which occurs due to insulin resistance, increases the intrahepatocytic fatty acids by increasing glycolysis and decreasing the apolipoprotein B-100, resulting in decreased export as VLDL and its accumulation in liver. The result is an increase in fatty acids and triglycerides in the hepatocytes, leading to steatosis.

The free fatty acids in the hepatocytes act as reactive oxygen species and increase the mitochondrial β-oxidation and cytochrome P-450 4A and cytochrome P450 2E1 levels.The mitochondrial oxidative stress leads to the second hit resulting in conversion of steatosis to steatohepatitis and fibrosis by three main mechanisms, namely (i) lipid peroxidation, (ii) cytokine induction, and (iii) Faslig and induction[82,84].

i. Lipid peroxidation: It causes oxidative destruction of polyunsaturated fatty acids in cellular membranes. The cytotoxic products released due to lipid peroxidation impair cellular functions, including nucleotide and protein synthesis, leading to cell death, formation of Mallory hyaline, promoting tissue inflammation, activation of stellate cells and collagen synthesis.[82]

ii. Cytokines like IL-1, IL-6 IL-8 and tumor necrosis factor-α (TNF-α) are important cytokines in the pathogenesis of liver injury in patients of NASH.[85]

IL-1, IL-6, and IL-8 are pro-inflammatory cytokines, and IL-10 and IL-12 are anti-inflammatory cytokines. TNF-α, TGF-β, and interleukin-8 cause chemotaxis, Mallory hyaline formation and collagen synthesis by activated stellate cells.

TNF–αdownregulates insulin-induced phosphorylation of insulin receptor substrate 1 and reduces the expression of the insulin-dependent glucose transport molecule Glut 4 and thus contributes towards insulin resistance which is thought to be one of the major mechanism in the pathogenesis of NASH.[85,86].

TNF-α is derived from adipose tissue. Plasma levels of TNF-αalso correlate with body fat mass and have also been found to be associated with insulin resistance[87].TNF-α knockout mouse also fails to develop insulin resistance after induction of obesity, suggesting its important role in the pathogenesis of insulin resistance.[88]The oxidative stress leads to the IkKβ activation which

release TNF- α and causes insulin resistance, which ultimately leads to steatohepatitis.

iii. Finally, the expression of Fas ligand due to oxidative stress leads to fractional killing by interaction with Fas on other hepatocytes.

Other factors that are involved in the pathogenesis of NASH include serum and liver iron[89,90] leptin,[91] bacterial overgrowth[92,93,88] Saturation of mitochondrial β-oxidation leads to peroxisomal oxidation and generation of hydrogen peroxide, which in the presence of increased iron gets converted to hydroxyl radicals, thus adding to the oxidative stress and further injury and steatosis[93].

Leptin leads to hepatic steatosis by promoting insulin resistance or modulating insulin signalling in hepatocytes.[90]

Bacterial overgrowth in the gut can result in liver injury by causing endotoxemia and release of cytokines. The mechanisms by which intestinal bacteria may increase hepatic oxidative stress are increased endogenous production of ethanol and by direct activation of inflammatory cytokines in luminalepithelial cells, and liver macrophages or both[91].

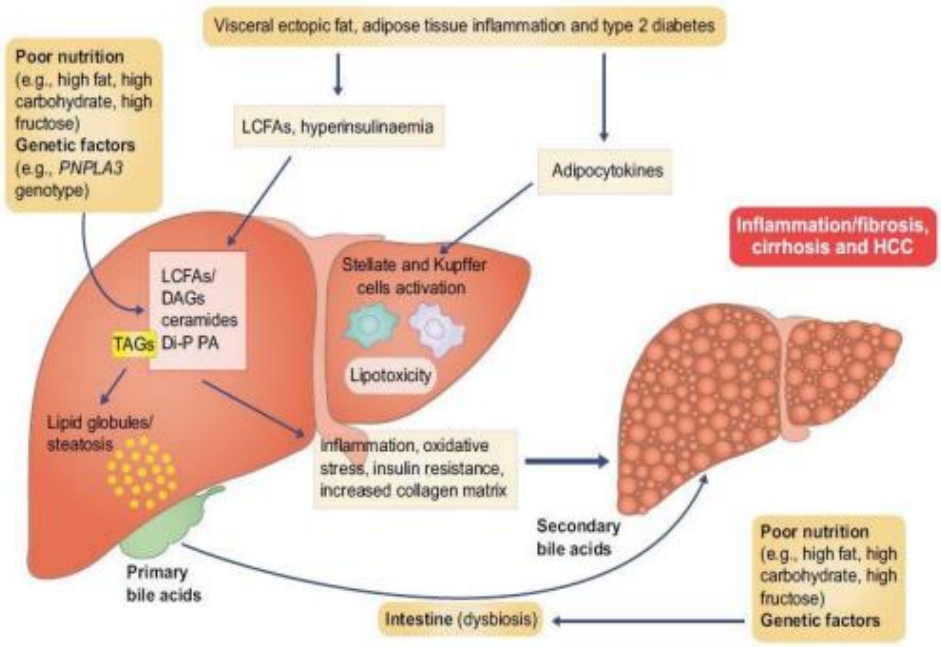


Figure 1 : ETIOPATHOGENSIS OF NAFLD-

The factors like visceral ectopic fat accumulation, adipose tissue inflammation, type 2 diabetes and intestinal dysbiosis promote the development of progressive liver disease in NAFLD. (Non-Alcoholic Fatty Liver Disease)

Review of Related Literature

Huber et al., (2022)[94] This study was aimed to examine liver enzymes and surrogate scores of hepatic steatosis and advanced hepatic fibrosis in a German population. In this study, 19.9% of ALT, 12.8% of AST, and 14% of GGT were abnormally high. Use of alcohol and the presence of metabolic syndrome both increase the chance of developing liver disease. According to the FLI, 37.5 percent of the population had hepatic steatosis, 1.1 percent of patients had a FIB4 greater than the upper threshold, and 19.2 percent fell somewhere in the middle. Males had a higher prevalence of advanced fibrosis than females, in this study. Furthermore, in the

current study sample, older age was associated with a noninvasive surrogate score indicative of advanced fibrosis. Nearly 20% of Germans had abnormally high levels of liver enzymes. Advanced fibrosis has been projected to affect one percent of the German population.

Thong et al., (2021)[95] The purpose of this study was to examine the relationship between NAFLD and liver stiffness in Vietnamese patients by measuring blood alanine aminotransferase and aspartate transaminase levels. Transient elastography was used to evaluate the stiffness of the liver. Participants' demographic, laboratory, and histopathology information was also gathered. NAFLD patients were divided into groups based on their serum ALT levels and their baseline and clinical features were compared. Of the total NAFLD patients, 138 (50.4%) were men, while 40.6% were women (mean SD age, 41 11 years). No statistically significant difference was seen in the liver fibrosis (F0) levels between the two groups ($p = 0.469$).

Similarly, there was no significant difference between the two groups regarding the prevalence of moderate fibrosis (F2) ($p = 0.371$). NAFLD patients with advanced fibrosis (F3, F4) had significantly higher ALT levels (3.2% vs. 15.9%, $p = 0.0013$; 3.2% vs. 13.2%, $p = 0.0047$). The sensitivity and specificity of the 59 U/L cut-off value for diagnosing NAFLD patients with minimal to moderate fibrosis (F1-F2) were 67% and 51%, respectively. There was a cut-off value of 81 U/L with 53% sensitivity and 67% specificity in individuals with severe fibrosis and cirrhosis (F3-F4). Patients at high risk for developing progressive and severe hepatic disease would be misclassified as having mild NAFLD if ALT levels were used as a diagnostic for severe NAFLD. There results demonstrate the limited value of ALT as a standalone factor in diagnosing NAFLD severity.

Campos-Murguía et al., (2020)[96] Through an analysis of the current literature, there study intended to suggest a workable and sequential

strategy for evaluating and treating liver fibrosis in individuals with NAFLD. Clinical, genetic, and environmental drivers of fibrosis formation and progression must be identified in evaluating patients with NAFLD. Detecting fibrosis requires a systematic strategy that begins with the best available biochemical scores, continues with a complementing imaging examination (transient elastography, magnetic resonance elastography, or an acoustic radiation force impulse), and, if necessary, concludes with a liver biopsy. There review provides Fagan's nomogram analysis, summarising the diagnostic yield of each method and their post-test chance of identifying liver fibrosis, to aid in selecting the best-suited approach. Last but not least, patients with severe fibrosis or high risk of advancement should be allocated into clinical trials where possible in addition to receiving standard care (including diet and exercise) and control of the components of the metabolic syndrome (with or without vitamin E). The ultimate goal is to establish an appropriate diagnosis and treatment of liver fibrosis in patients with NAFLD, with the hopes of reducing or halting the advancement of hepatic fibrosis and improving their prognosis.

Goh et al., (2015)[97] The goal of this study was to examine the age-related differences in NAFLD's clinical and histological features. There were 502 patients with biopsy-proven NAFLD included in this prospective cross-sectional analysis. Clinical data from three age groups (18-44, 45-64, and 65+) were analysed and compared (Cages 65). Group A had 34.9% of the cohort, Group B had 56.0%, and Group C had 9.1%. However, the incidence of severe fibrosis rose sharply with age (p 0.0001), although nonalcoholic steatohepatitis (NASH) remained similar across age groups. Though there was a significant age-related decline in mean ALT levels (87, 64, and 56 U/L in groups A, B, and C, respectively; p = 0.000), there was no difference in mean AST levels (p = 0.939). In groups A, B, and C, the AST:ALT ratio (AAR) improved from 0.70 to 0.90 to 1.10 (p = 0.000). Seventy-four percent and forty percent of patients in group C with and

without severe fibrosis, respectively, had an AAR C1. Age was associated with a rise in AAR due to the steady rise in AST levels and the steady reduction in ALT levels. Greater AAR is frequently utilised as a proxy for more severe fibrosis, however, AAR can also rise with age.

Sanyal et al., (2015)[98] The purpose of this study was to compare liver enzyme profiles between people with impaired glucose tolerance (IGT), newly diagnosed, treatment-naive type 2 diabetes (T2DM), and normal glucose tolerance (NGT) with and without NAFLD. Clinical research is conducted at random intervals. Researchers compared 152 people with IGT, 158 people with newly diagnosed T2DM, and 160 controls with NGT, all ranging in age from 30 to 69 years. All patients underwent an ultrasonographic scan of the upper abdomen to check for fatty liver. All patients also had analyses of anthropometry, lipid profile, and liver enzymes. Find statistically significant differences, associations, and correlations between two or more groups using the unpaired t-test, Chi-square/Fisher Exact test (for categorical variables), and the Pearson/Spearman correlation test. Higher levels of alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) but not alanine aminotransferase (ALP) were found in people with IGT and typed 2 diabetes who also had NAFLD. A homeostatic model assessment found significant correlations between ALT and GGT and waist circumference, BMI, fasting insulin, insulin resistance, fasting blood glucose, HDL cholesterol, and triglyceride levels. The ALT levels of 57% of NAFLD patients and the GGT levels of 53% of NAFLD subjects were within the normal range (25-40 U/L and 15-30 U/L, respectively). In there study, Maximum negative predictivity for the existence of NAFLD was seen for ALT 25 U/L and GGT 15 U/L, and the highest positive predictivity was seen for ALT >40 U/L and GGT >30 U/L. Patients with IGT and newly diagnosed T2DM can have NAFLD and metabolic syndrome characteristics with mild increases of liver enzymes in the normal upper range. New liver enzyme cutoffs are needed to prevent unnecessary

diagnostic workups and to detect NAFLD early, which can lower the risk of cirrhosis, hepatocellular carcinoma, and classical cardiovascular disease in people with type 2 diabetes and impaired glucose tolerance.

Neuman et al., (2014)[99] study was done To examine the diagnostic and severity biomarkers for NAFLD and NASH. Non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, and the names of all known biomarkers were utilised in a comprehensive medical literature search using PubMed and Google Scholar. They used indexing data from 2004 to 2014. Disease appearance and progression may be tracked with the help of biomarkers. Total cholesterol, triglyceride, insulin resistance, and C-peptide are only some of the serum biomarkers that have been utilised for decades. Several novel biomarkers have been postulated as potential complements to more established ones, including apolipoprotein A1, apolipoprotein B, leptin, adiponectin, free fatty acids, ghrelin, and tumour necrosis factor-alpha.

Additionally, cytokeratins, indicators of cell death and mitochondrial dysfunction, are robust risk predictors. Accurately identifying and treating diseases with biomarkers requires age-specific reference intervals that consider changes in sex and ethnicity. This study thoroughly examinedthe developing risk biomarkers of NAFLD and NASH, highlighting sentinel signs of disease progression based on their clinical importance and analytical concerns.

Kneeman et al., (2012)[100]Nonalcoholic fatty liver disease (NAFLD) was described as 17–30% prevalent in developed countries and 2-4% worldwide, making it the leading cause of chronic liver disease in regions still emerging from poverty. A group of diseases from simple steatosis to nonalcoholic steatohepatitis, NAFLD is defined as the buildup of fatty acid content greater than 5% of liver weight. Increased hepatocyte de novo fatty acid production and lipid retention due to decreased hepatocyte

apolipoprotein secretion or beta-oxidation are central to the pathogenesis of NAFLD. Obesity, type II diabetes, dyslipidemia, and insulin resistance are well-known major factors of NAFLD. However, in patients who appear with NAFLD but do not have typical risk factors, it is important to investigate the possibility that other, less frequent diseases are responsible for the patient's clinical and histologic presentation. In there review, they examined the less prevalent but still essential causes of NAFLD, such as inborn errors of metabolism, iatrogenic causes, viral hepatitis, and nutritional problems, to help practising doctors better treat their patients.

Uslusoy et al., (2011)[101] study done to assess noninvasive markers of liver fibrosis in nonalcoholic steatohepatitis by analysing anthropometric, clinical, and laboratory aspects indicative of liver fibrosis. Forty-one male and forty-one female patients who had been diagnosed with fatty liver via ultrasonographic examination and met inclusion criteria took part in there study. After receiving informed consent, they recorded each case's anamnestic, anthropometric, clinical, and laboratory characteristics. Age 45, gender, body mass index, central obesity, aspartate aminotransferase (AST) > ALT, -glutamyltransferase (GGT) > ALT, platelet count, insulin, c-peptide levels, and the presence of hypertension, diabetes, hypertriglyceridemia, and insulin resistance were all taken into consideration when analysing steatosis, necroinflammation, and liver fibrosis. Eighty-one patients with NASH participated in the research. In 81 patients, 69 were identified as having NASH, 11 as having plain fatty liver, and 1 as having cirrhosis. Steatosis, necroinflammation, and fibrosis appeared to be exacerbated by high serum ferritin and fasting insulin levels, diabetes, hypertension, hypertriglyceridemia, and insulin resistance. However, these results were not statistically significant. Even at a healthy weight, some people develop liver fibrosis and steatosis. In there study the severity of liver histology did not correlate with the presence of predictors for liver fibrosis, such as metabolic risk variables.

Prashanth et al., (2009)[102] In this study, prevelance and risk factor of NAFLD in individuals with type 2 diabetes were seen. Patients with type 2 diabetes mellitus who were seen in an outpatient clinic were scanned using abdomen sonography (n = 204). Of the 127 individuals with ultrasound-detected fatty infiltration, 90 agreed to have a liver biopsy, clinical, and biochemical evaluation. Histological examination revealed NAFLD in 87.0%, including steatohepatitis in 62.6% and fibrosis in 37.3%. The existence or severity of NAFLD or fibrosis was not predicted by age, length of diabetes mellitus, degree of glycemic control, body mass index, waist circumference, or a family history of diabetes mellitus. Although still within normal ranges, the levels of alanine aminotransferase (ALT) and alkaline phosphatase in the serum of patients with steatohepatitis were noticeably higher. The presence of more symptoms of the metabolic syndrome was associated with a higher incidence of nonalcoholic steatohepatitis. Patients with extensive fibrosis also had a significantly higher serum AST/ALT ratio (p=0.049). Metabolic syndrome was present in 100% of patients with severe fibrosis. The prevalence of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) was significant in there sample of individuals with type 2 DM.

Gramlich et al., (2004)[103] Histological fibrosis is a hallmark of NAFLD, and this investigation focuses on the clinical and pathological aspects of patients with NAFLD who experience this complication. By searching there NAFLD database, which includes detailed clinical, demographic, and laboratory information, theycould identify patients with a confirmed diagnosis of nonalcoholic fatty liver disease.

Different forms of histological fibrosis were linked to the collected clinical and pathological data. Histological fibrosis risk factors were identified using univariate and multivariate analysis. Twenty-one percent of 132 patients with NAFLD had cirrhosis or advanced fibrosis (septal/bridging fibrosis or cirrhosis). Twenty-three percent of patients had sinusoidal

fibrosis, while only seventeen percent of patients had perivenular fibrosis. Sinusoidal and perivenular fibrosis were independently connected to ballooning degeneration and Mallory bodies. Periportal-portal fibrosis was independently linked with aspartate aminotransferase/alanine aminotransferase ratio and ballooning degeneration. They infer that fibrosis is linked to the existence of hepatocyte damage in NAFLD. A histological diagnosis of NAFLD or NASH progression can be made using these findings.

MATERIALS AND METHODS

Study Site-

The study was carried out in Department and O.P.D. of Medicine and Gastroenterology, Dayanand Medical College and Hospital Ludhiana

Study Type –

Prospective Observational Study

Source Of Data

All the patients in o.p.d and in department of medicine and gastroenterology with NAFLD , with advanced fibrosis on transient elastography and have mildly elevated transaminases .

Method Of Collection Of Data

Inclusion Criterion-

- Age >18 years
- Non Alcoholics
- Advance fibrosis on transient elastography
- Transminases levels < 5 times the upper limit of normal
- Patient who give the consent for the study

Exclusion Criterion

- Patient who don't give the consent for the study
- Age<18 years
- Alcoholic liver disease
- Fibrosis due to viral liver disease
- Haemochromatosis , wilsons disease
- PBC , PSC, Autoimmune hepatitis

Non-alcoholic fatty liver disease (NAFLD) is defined by macrovesicular steatosis in ≥5% hepatocytes, in the absence of a secondary cause such as alcohol or drugs. It encompasses a spectrum of disease from non-

alcoholic fatty liver (NAFL) through to non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis.

The patients who were diagnosed with NAFLD and had advanced fibrosis on transient elastography were included in the study after the informed consent of the individual.

According to NCEP ATP III definition, metabolic syndrome is present if three or more of the following 5 criteria are met:

a) waist circumference >102cm for men, >88cm for women
b) Blood pressure >130/85mmhg
c) Fasting triglycerides >150mg/dl
d) HDL <40mg/dl in men and < 50mg/dl in women
e) fasting blood sugar >100mg/dl

BMI according to Asian pacific guidelines was taken –

TABLE 1- BMI according to Asia pacific guidelines-

CATEGORY	BMI KG/M^2
UDERWEIGHT	<18.5
NORMAL	18.5-22.9
OVERWEIGHT	23-24.9
OBESE	>25

Waist circumference of >94cm for male and >80 cm for female was considered as a risk factor for metabolic complication (as per WHO cut off for risk of metabolic complications).

Lipid profile parameters were taken according to the lab refrence range value.

HOMA-IR was calculated using the formula – fasting insulin x fasting glucose /22.5 and value of >2.5 was taken as a marker of isnulin resistance.

A prospective observational study was carried on all the patients.
Information from the patient was collected through a pre designed Performa for each patient being enrolled in the study.
Laboratory parameters were collected from patients medical records and refrence range was consider according to lab refrence value.
Proper history , anthropometric data ,was collected from the patients .
Root cause analysis was done. Various risk factors leading to non alcoholic fatty liver disease were identified.

Duration of Study/ Number of Cases

12 months

Outcome –

Analysis of risk factor of NAFLD with advanced fibrosis with mild elevation of transaminases level.

Statistical Analysis (Name of the method in plan)

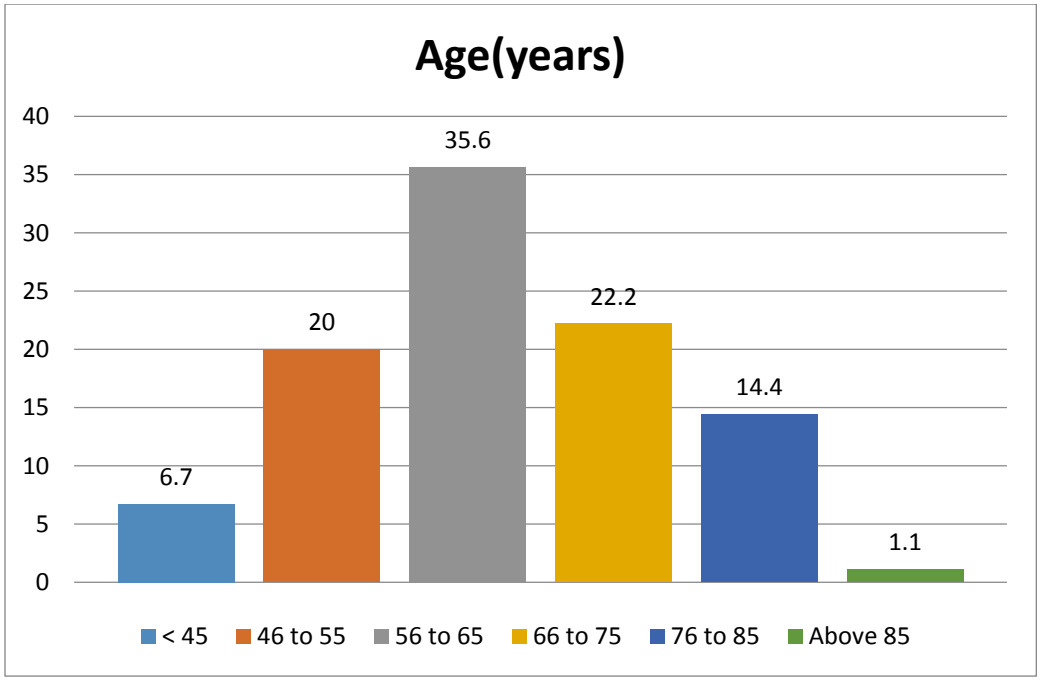
Prospective Observational study was carried out on OPD and IPD patients of NAFLD in Medicine and Gastroenterology department, from 1st March 2021 to 28th February,2022.
Data was described in terms of range, mean +/- Standard Deviation (+/- SD), median, frequencies, (number of cases) and relative frequencies (percentages) as appropriate. All statistical calculations were done using (statistical package for social science) SPSS 21 Version (SPSS Inc., Chicago, IL, USA) statistical programme for Microsoft Windows.

OBSERVATIONS & RESULTS

TABLE 2: AGE DISTRIBUTION (YEARS)

AGE (years)		
	Frequency	Percent
< 45	6	6.7
46 to 55	18	20.0
56 to 65	32	35.6
66 to 75	20	22.2
76 to 85	13	14.4
Above 85	1	1.1
Total	90	100.0

FIGURE 2: AGE DISTRIBUTION (YEARS)



From the above table and graph it was observed that majority of the patients (35.6%) belongs to age group 56 to 65 years followed by 22.2% patients of age group 66 to 75 years. These findings suggest that majority of patients belongs to upper-middle age group.

TABLE 3: AGE DESCRIPTIVE STATISTICS (YERARS)

Age Descriptive Statistics (yeras)	
Mean	**Std. Deviation**
63.0111	11.11179

From the above table and graph it was observed that mean age of the patients was 63.01±11.11 years.

FIGURE 3: AGE DESCRIPTIVE STATISTICS (YERARS)

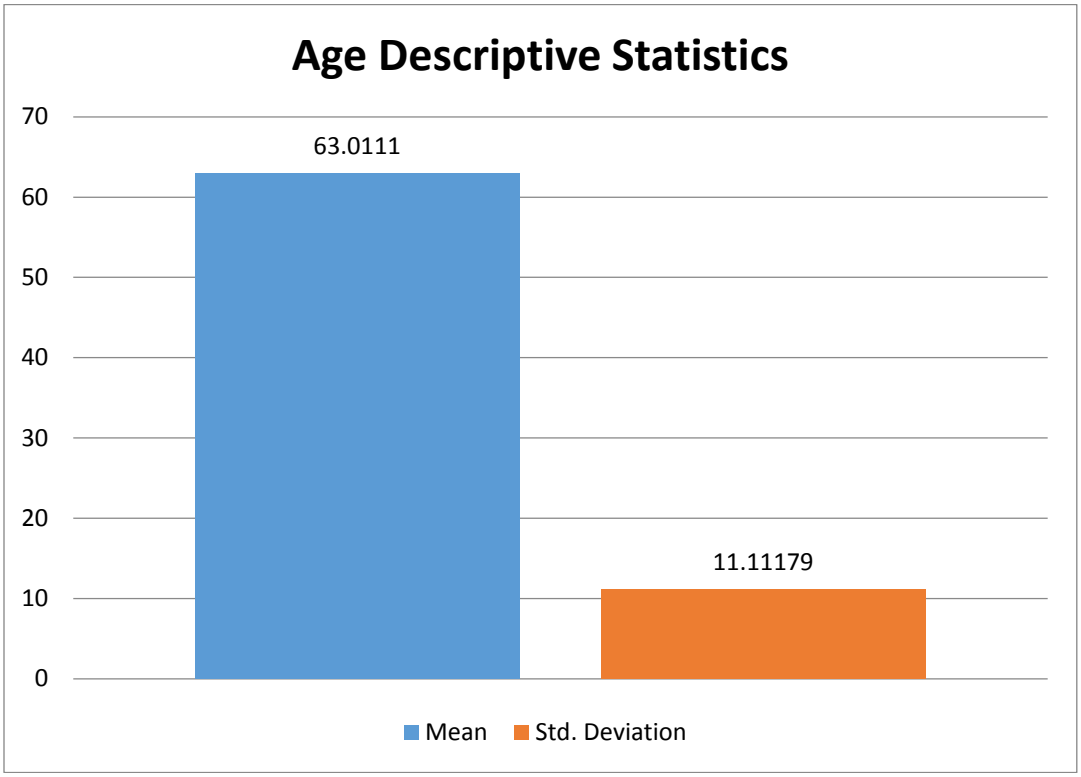


TABLE 4: GENDER DISTRIBUTION

Gender		
	Frequency	Percent
Male	49	54.4
Female	41	45.6
Total	90	100.0

From the above table and graph it was observed that there was 54.4% males and 45.6% females. These findings suggest that the study population is dominated by male patients.

FIGURE 4: GENDER DISTRIBUTION

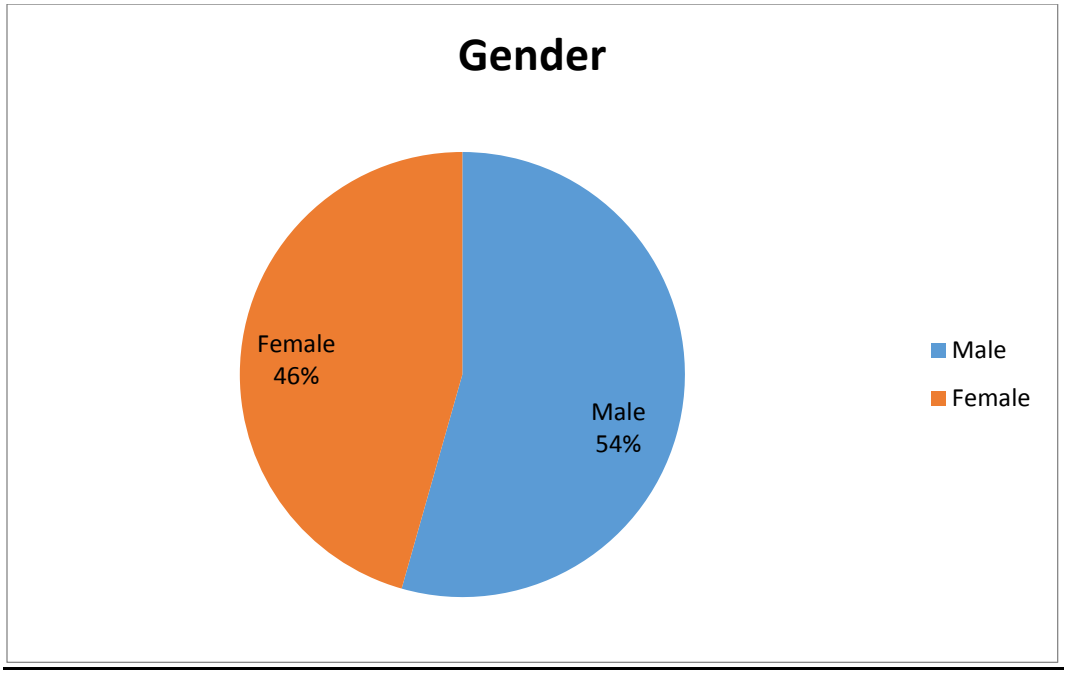


TABLE 5: OCCUPATION

Occupation		
	Frequency	Percent
Business	13	14.4
Dependent	13	14.4
Farmer	11	12.2
Government employee	3	3.3
Housewife	28	31.1
Laborer	2	2.2
Lawyer	1	1.1
Self Employed	3	3.3
Shopkeeper	16	17.8
Total	90	100.0

From the above table and graph it was observed that majority of the patients (31.1%) were housewife, followed by 17.8% patients who were shopkeeper. The study found out that there were 14.4% business person and 14.4% dependent patients.

FIGURE 5: OCCUPATION

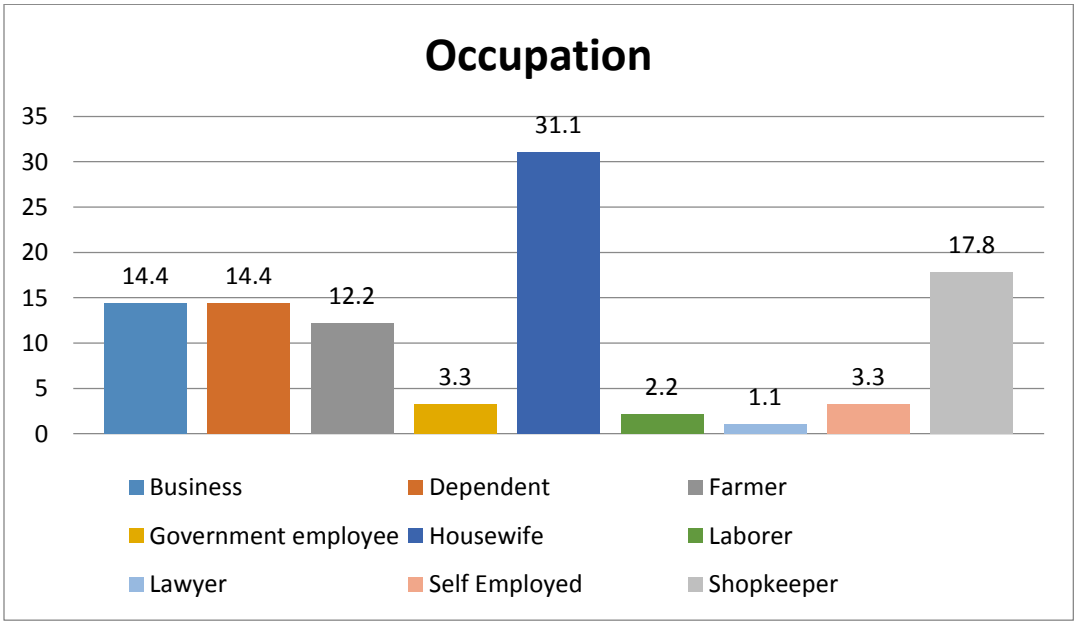


TABLE 6: DIABETES MELLITUS STATUS WITH ADVANCED FIBROSIS IN NAFLD

Diabetes Mellitus			
	Frequency	Percent	P Value
Yes	71	78.9	0.000
No	19	21.1	
Total	90	100.0	

From the above table and graph it was observed that 78.9% patients were diabetic while 21.1% patients were non diabetic. These findings suggest that in our study population majority of patients were diabetic.

FIGURE 6: DIABETES MELLITUS STATUS WITH ADVANCED FIBROSIS IN NAFLD

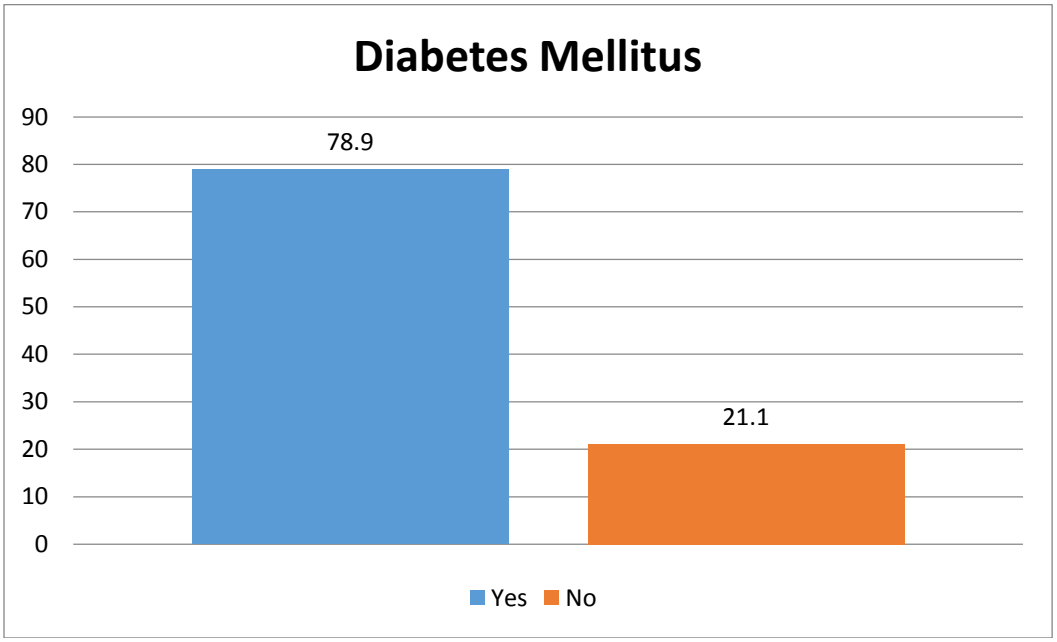
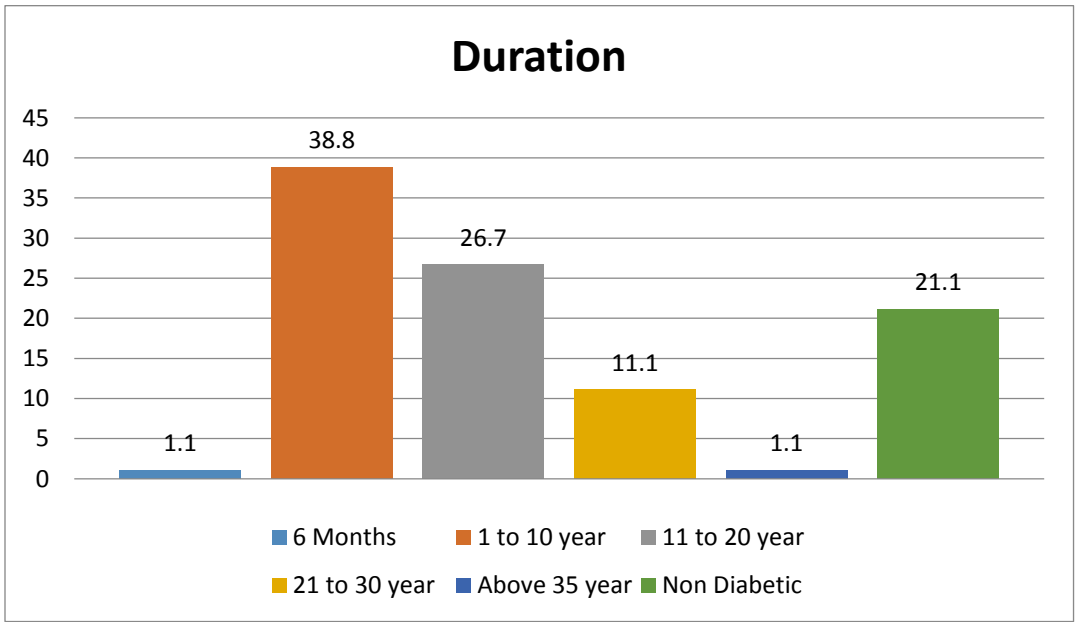


TABLE 7 : DURATION AND TREATMENT OF DIABETES MELLITUS

Diabetes Mellitus		
Duration		
	Frequency	**Percent**
6 Months	1	1.1
1 to 10 year	35	38.8
11 to 20 year	24	26.7
21 to 30 year	10	11.1
Above 35year	1	1.1
Non Diabetic	19	21.1
On Diet /Drug Therapy		
ON Insulin	17	23.95
ON OHA	54	76.05

From the above table and graph it was observed that majority of the patients(38.8%) have diabetes for 1 to 10 years, followed by 26.7% patients who had diabetes for 11 to 20 years. There were only one patients who had diabetes for a duration of more than 35 years.

FIGURE 7: DURATION OF DIABETES MELLITUS



From the above table and graph it was observed that 23.95% patients were on insulin while 76.05% patients were on OHA. These findings suggest that in our study population majority of patients were treated using OHA.

FIGURE 8: TREATMENT REGIME FOR DIABETES MELLITUS

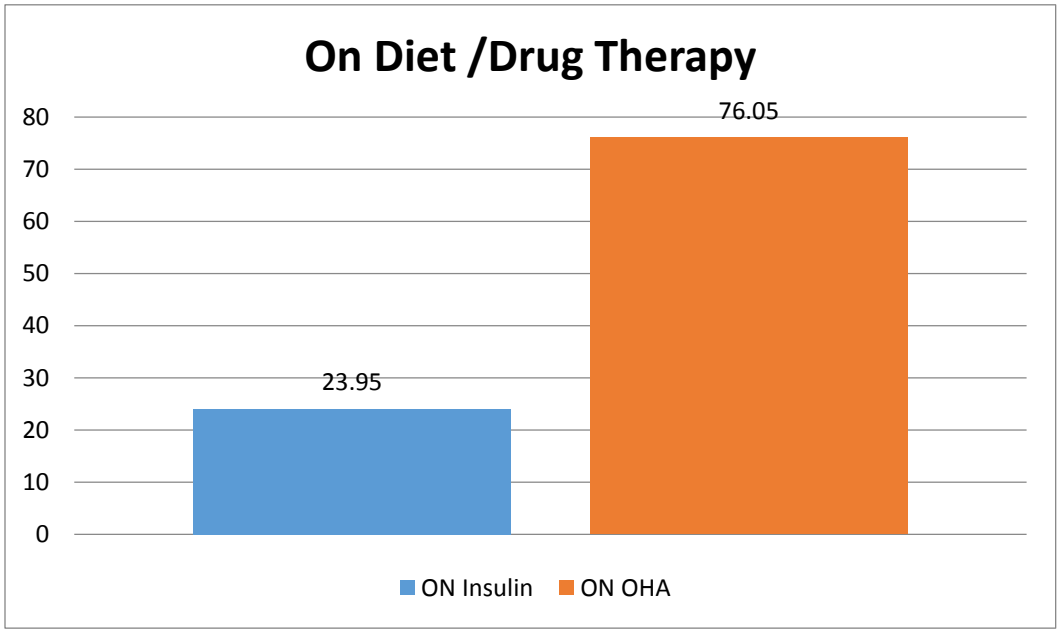


TABLE 8: MEAN HbA1C LEVELS (%) IN PATIENTS WITH ADVANCED FIBROSIS IN NAFLD

Hba1c Levels(%)		
Mean	**Std.**	**P Value**
8.94	1.60	0.899

From the above table and graph it was observed that mean HbA1c was 8.94±1.60 % which showed uncontrolled glycemic status.

FIGURE 9: MEAN HbA1C LEVELS (%) IN PATIENTS WITH ADVANCED FIBROSIS IN NAFLD

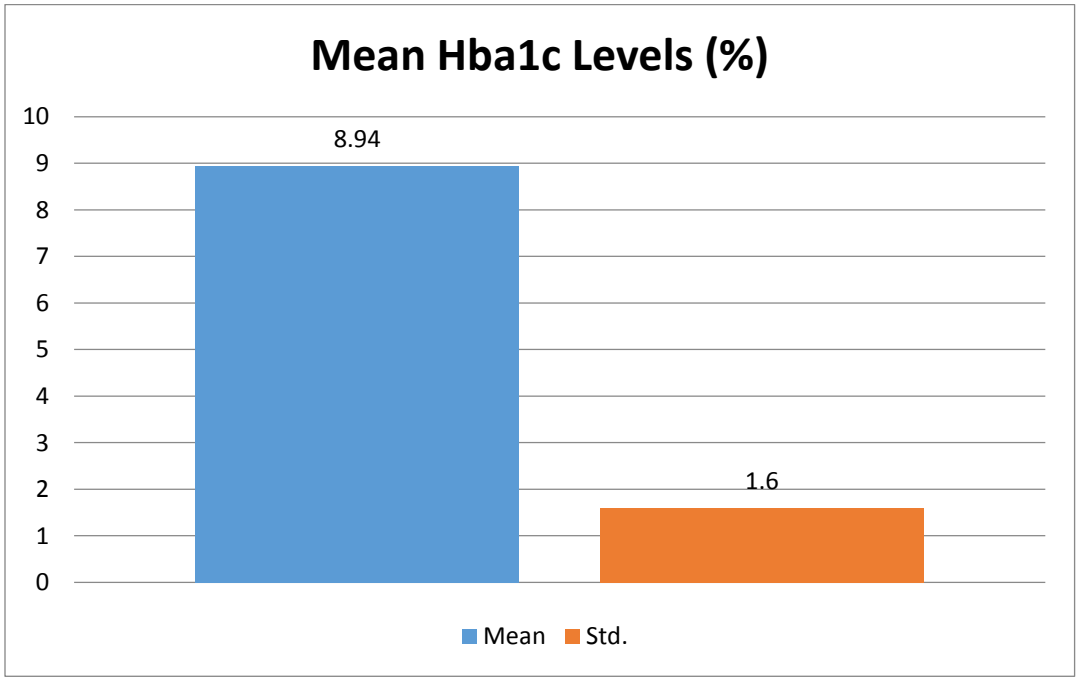


TABLE 9: LIPID PROFILE PARAMETERS(mg/dl)

Lipid Profile Parameters(mg/dl)		
	Mean ± Std.	**P Value**
LDL Levels	128.51± 35.54	0.899
HDL Levels	33.00 ± 10.59	1.000
Total Cholesterol	241.28 ± 58.51	0.05
Triglycerides	238.08 ± 60.01	1.000

The above table and graph present the lipid profile findings of the study subjects. From the above table and graph it was observed that mean LDL levels was 128.51± 35.54 mg/dl, HDL level was 33.00 ± 10.59 mg/dl, Total Cholesterol was 241.28 ± 58.51 mg/dl, and triglycerides was238.08 ± 60.01 mg/dl.

FIGURE 10: LIPID PROFILE PARAMETERS (mg/dl)

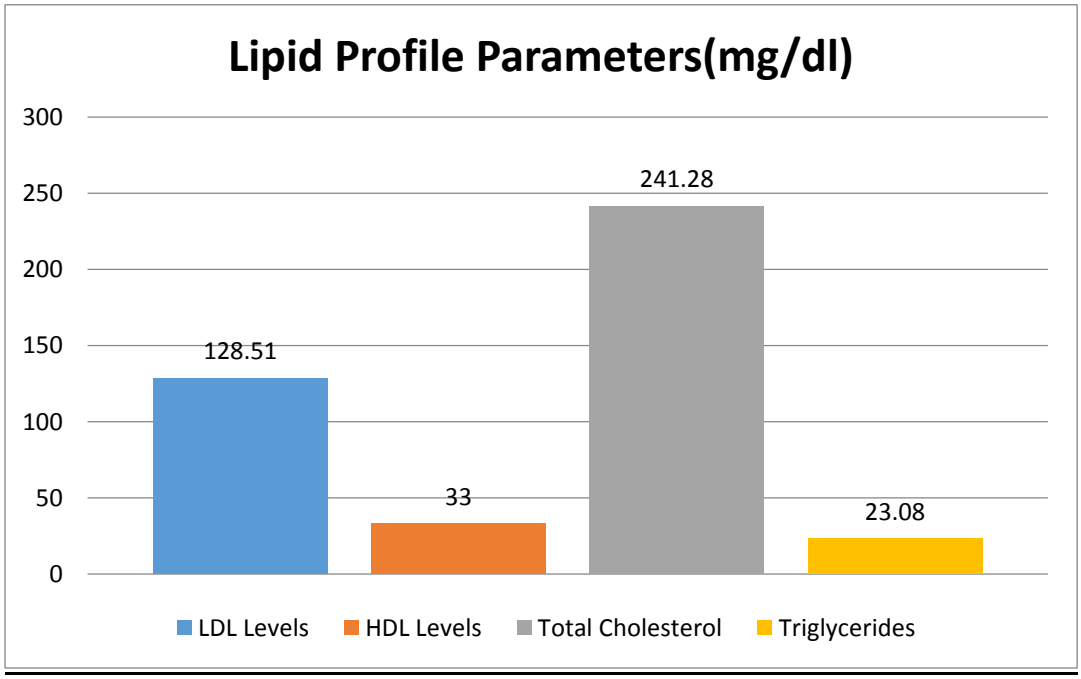


TABLE 10: LDL LEVELS>130mg/dl IN PATIENTS WITH ADVANCED FIBROSIS IN NAFLD

LDL levels >130mg/dl		
	Frequency	Percent
Yes	45	50.0
No	45	50.0
Total	90	100.0

From the above table and graph it was seen that 50% of patient had the LDL level above the higher upper limit of the reference range.

FIGURE 11: LDL LEVELS >130mg/dl IN PATIENTS WITH ADVANCED FIBROSIS IN NAFLD

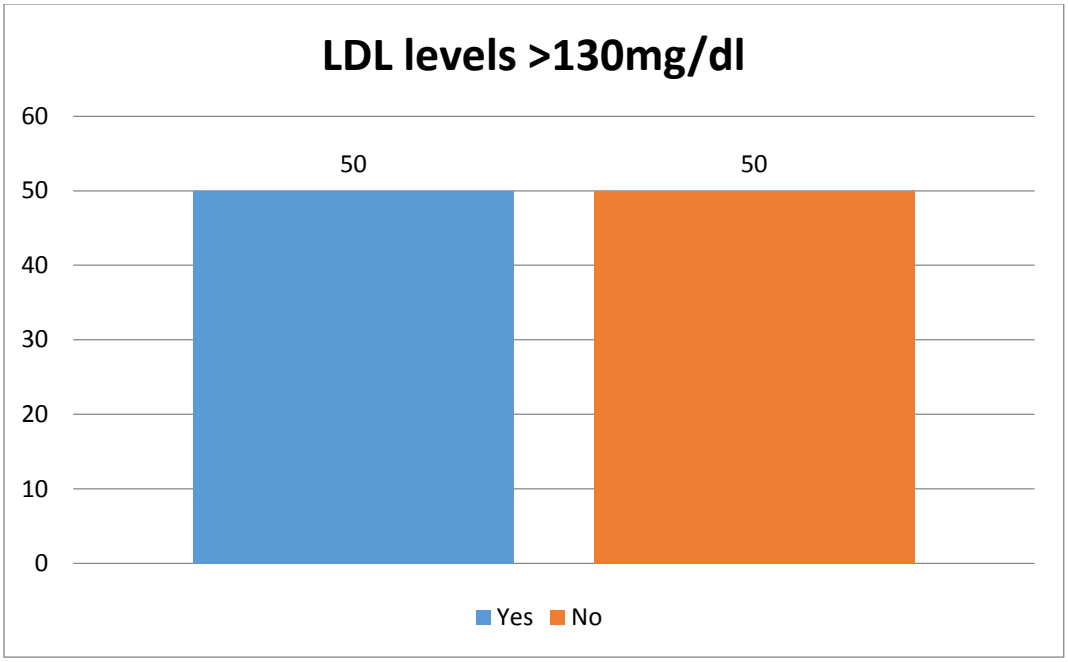


TABLE 11: HDL LEVELS <35mg/dl IN PATIENTS WITH ADVANCED FIBROSIS IN NAFLD

HDL Levels <35mg/dl		
	Frequency	Percent
Yes	51	56.7
No	39	43.3
Total	90	100.0

From the above table and graph it was seen that 56.7% patient had HDL levels below the lower limit of reference range.

FIGURE 12: HDL LEVELS <35mg/dl IN PATIENTS WITH ADVANCED FIBROSIS IN NAFLD

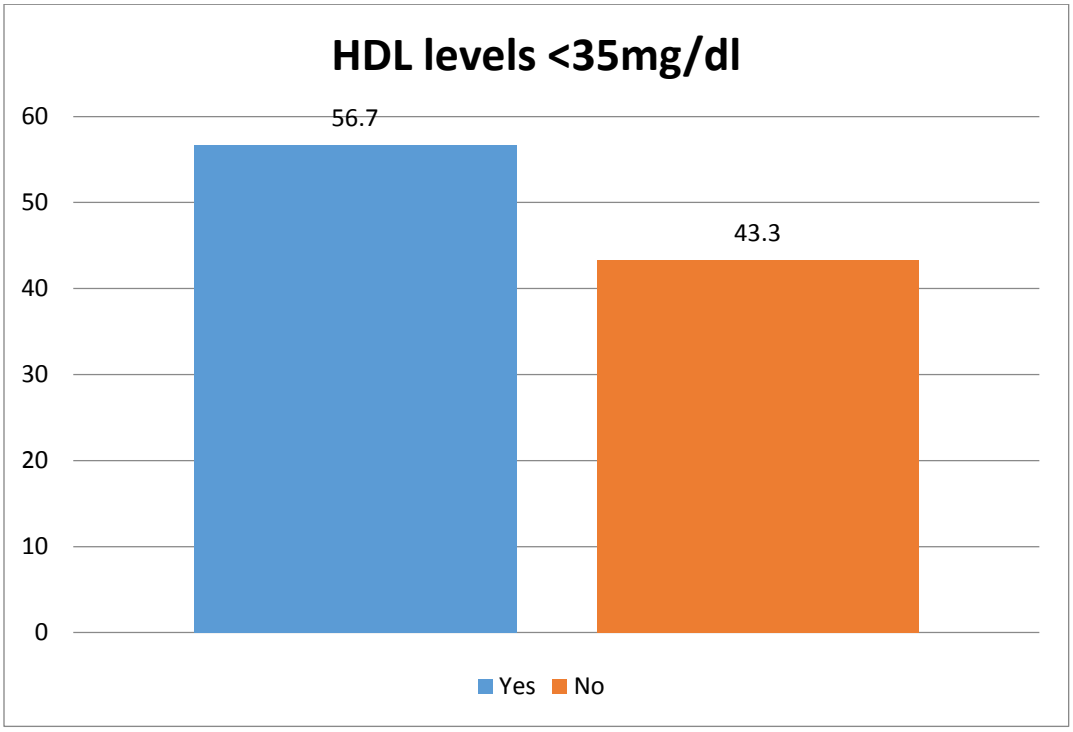


TABLE 12: TOTAL CHOLESTEROL >200 mg/dl IN PATIENTS WITH ADVANCED FIBROSIS IN NAFLD

Total cholesterol >200mg/dl		
	Frequency	Percent
Yes	69	76.7
No	21	23.3
Total	90	100.0

From the above table and graph it was seen that 76.7% patient had total cholesterol more than the upper limit of reference range.

FIGURE 13: TOTAL CHOLESTEROL > 200 mg/dl IN PATIENTS WITH ADVANCED FIBROSIS IN NAFLD

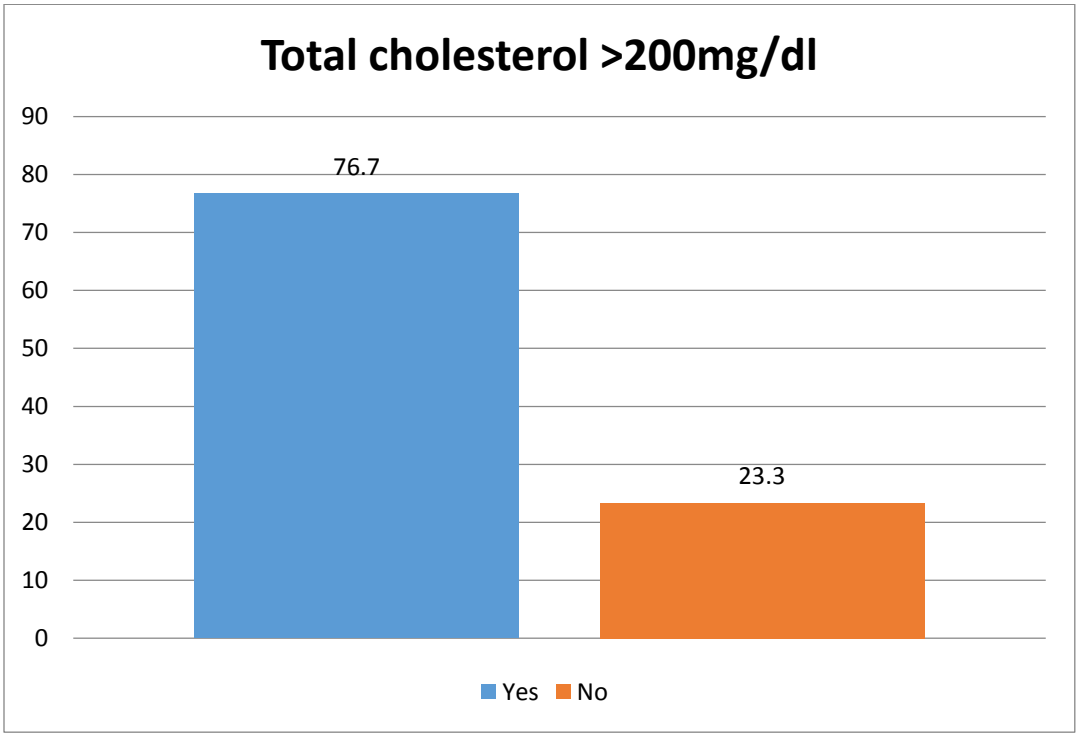


TABLE 13: TRIGLYCERIDES >200mg/dl IN PATIENTS WITH ADVANCED FIBROSIS IN NAFLD

Triglycerides >200mg/dl		
	Frequency	Percent
Yes	64	71.1
No	26	28.9
Total	90	100.0

From the above graph and table it was observed that 71.11% patient had triglyceride levels more than the higher upper limit of reference range.

FIGURE 14: TRIGLYCERIDES >200mg/dl IN PATIENTS WITH ADVANCED FIBROSIS IN NAFLD

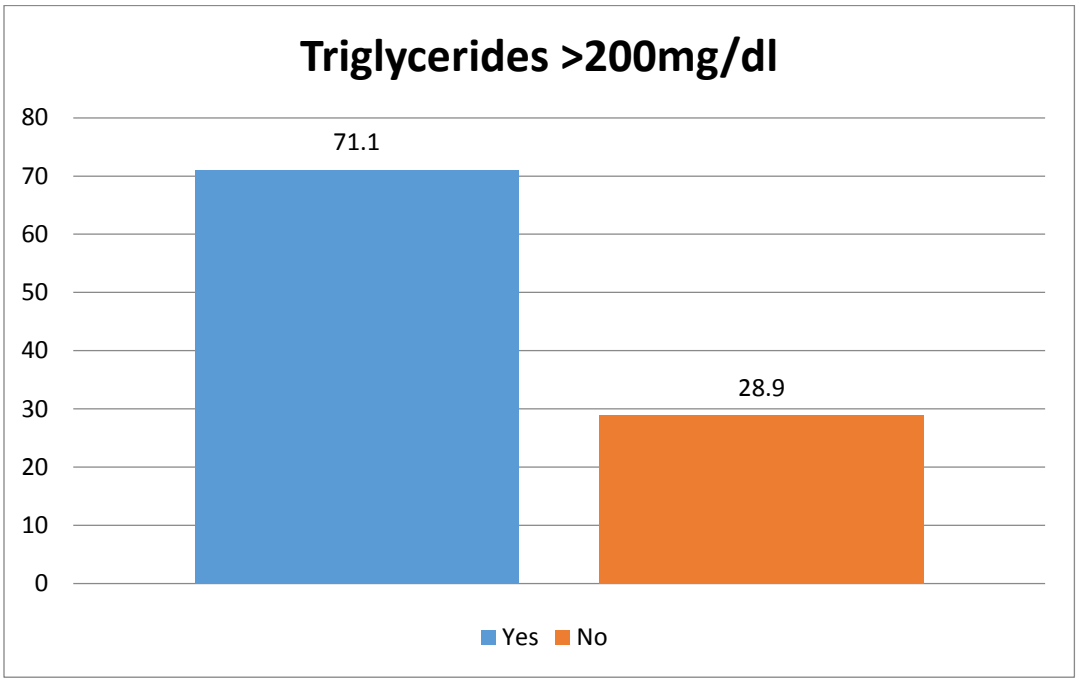


TABLE 14: ANTHROPOMETRIC PARAMETERS IN PATIENTS WITH ADVANCED FIBROSIS IN NAFLD

Anthropometric parameters		
	Mean ± Std.	**P Value**
BMI (kg/m^2)	27.39 ± 3.40	0.430
Weight(kg)	87.92 ± 12.69	0.130
Waist (cm)	98.74 ±13.10	0.23

From the above table and graph it was observed that mean BMI of the study subjects was 27.39 ± 3.40 kg/m^2. The study found out that mean weight was 87.92 ± 12.69 kgs, while mean waist circumference was 98.74 ± 8.95 cm.

FIGURE 15: ANTHROPOMETRIC PARAMETERS IN PATIENTS WITH ADVANCED FIBROSIS IN NAFLD

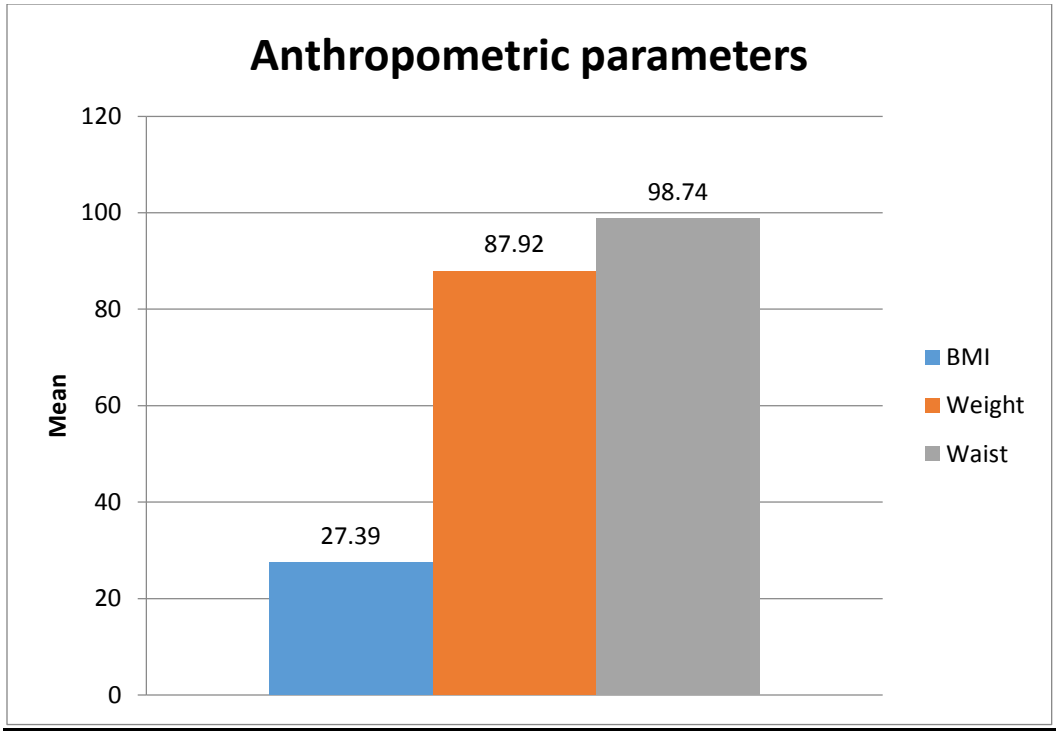


TABLE 15: BMI kg/m^2 IN PATIENTS WITH ADVANCED FIBROSIS IN NAFLD

BMI - kg/m2		
	Frequency	Percent
Normal	7	7.8%
Over Weight (23-24.9)kh/m2	11	12.2%
obese>/=25kg/m2	72	80.0%

From the above graph and table it was observed that out of patient who had advance fibrosis in NAFLD with mildly raised transaminases 7.8% patient had normal BMI , 12.2% patient were in over weight category and 80% patients were in obese category Asian pacific guidelines.

FIGURE 16: BMI kg/m^2 IN PATIENTS WITH ADVANCED FIBROSIS IN NAFLD

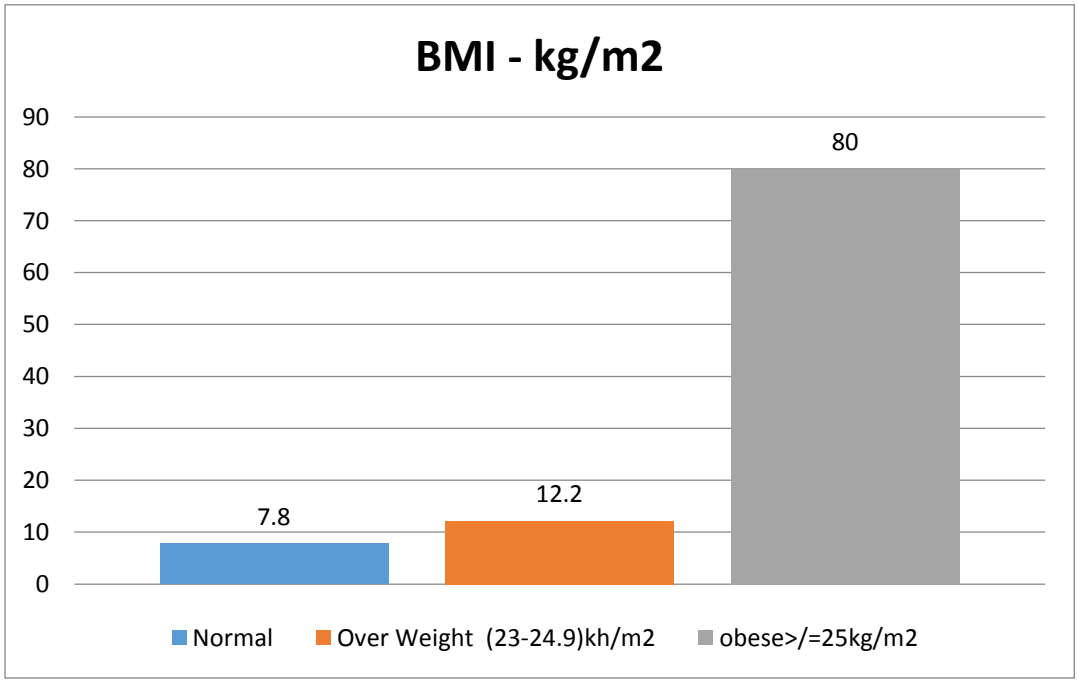


TABLE 16: WAIST CIRCUMFRENCE (CM) IN PATIENTS WITH ADVANCED FIBROSIS IN NAFLD

Waist Circumfrence (cm)			
	Frequency	Percent out of total	Percentage in each category
Men >94cm			
Yes	38	42.2%	77.5%
No	11	12.2%	22.5%
Female >80cm			
Yes	41	45.6%	100%

From the above table and graphs it was observed that around 77.5% men in men category had a waist circumference above the reference range for increased chances of metabolic complications and every female among female category had waist circumference above reference range.

FIGURE 17: WAIST CIRCUMFRENCE, MEN (CM)

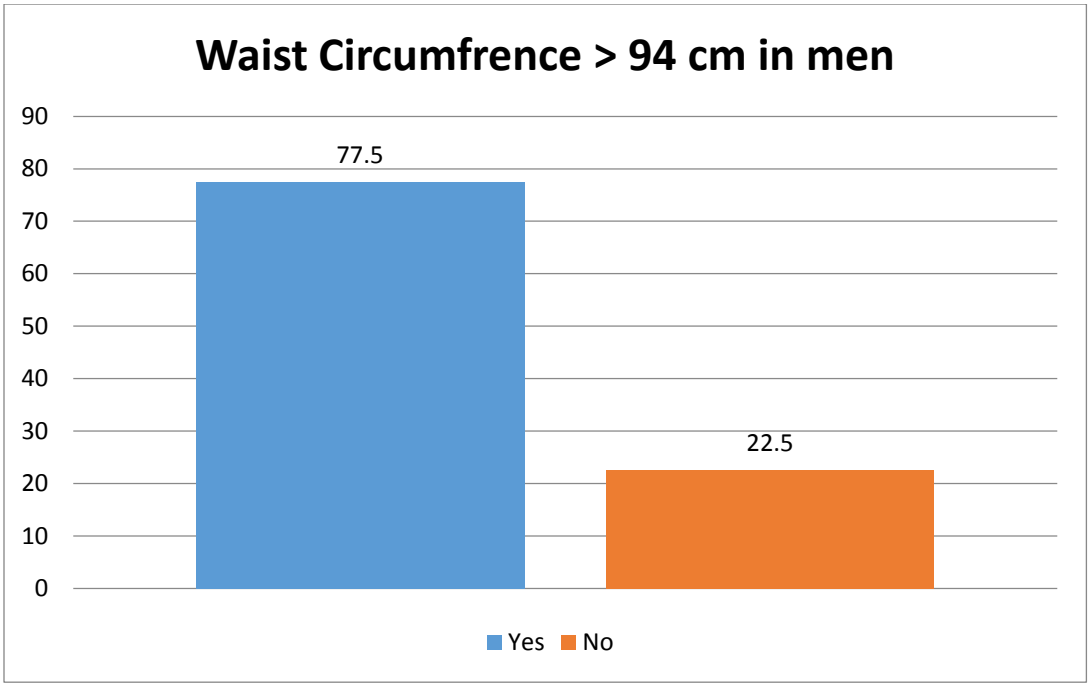


FIGURE 18: WAIST CIRCUMFRENCE, FEMALE (CM)

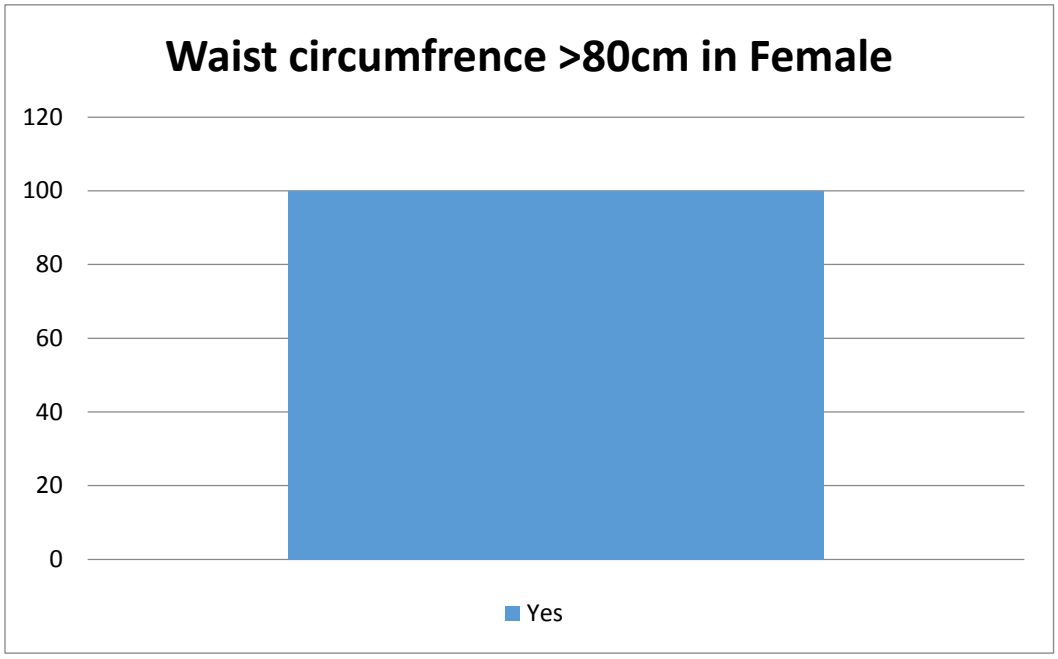


TABLE 17 : LAB PARAMETERS IN PATIENTS WITH ADVANCED FIBROSIS IN NAFLD

Lab Parameter	
	Mean ± Std.
Platelet Count (UL^{-1})	96755.56 ± 43945.40
AST Levels (U/L)	56.96±11.47
ALT Levels(U/L)	61.64 ± 12.19
AST/ALT Ratio	0.95 ± 0.2

The above table and graph present the lab parameters of the study subjects. From the above table and graph it was observed that mean platelet count was 96755.56 ± 43945.40 UL^{-1}, mean AST levels was 56.96 ±11.47 U/L, and ALT levels was 61.64 ±12.19 U/L. The study found out that AST/ALT Ratio was 0.95 ± 0.2.

FIGURE 19: LAB PARAMETERS IN PATIENTS WITH ADVANCED FIBROSIS IN NAFLD

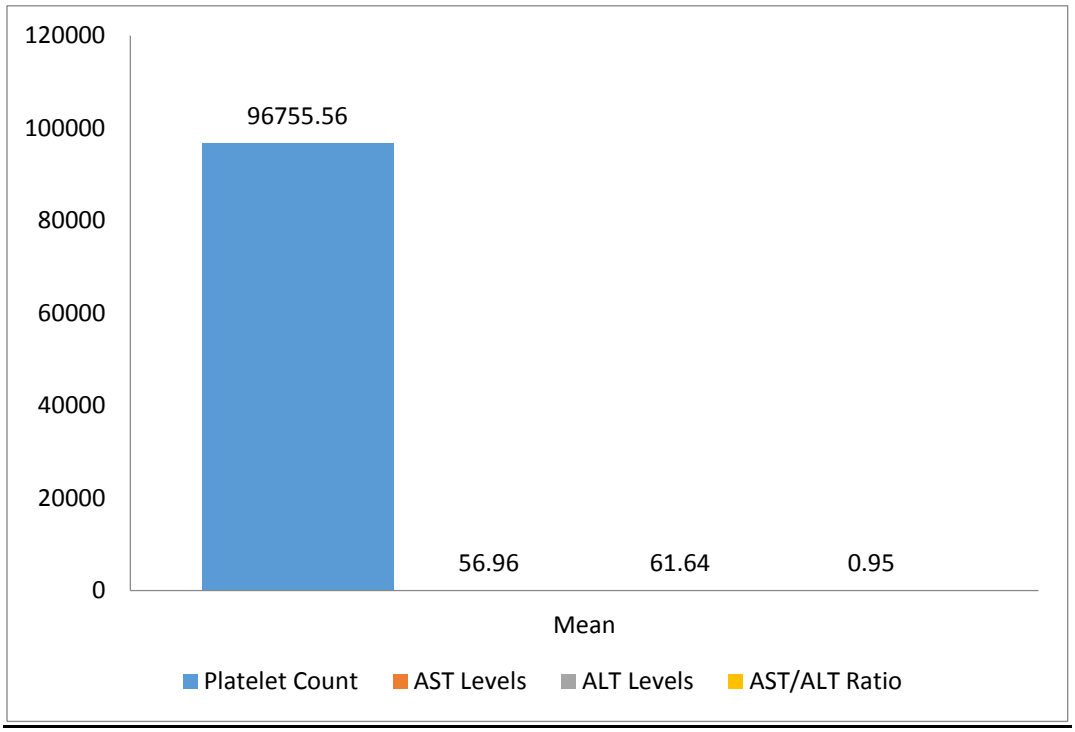


TABLE 18 :METABOLIC SYNDROME IN PATIENTS WITH ADVANCED FIBROSIS IN NAFLD

Metabolic Syndrome			
	Frequency	Percent	P Value
Yes	77	85.6	0.000
No	13	14.4	
Total	90	100.0	

From the above table and graph it was observed that metabolic syndrome was found in 85.6% patients while there were 13 patients free from metabolic syndrome.

FIGURE 20: METABOLIC SYNDROME IN PATIENTS WITH ADVANCED FIBROSIS IN NAFLD

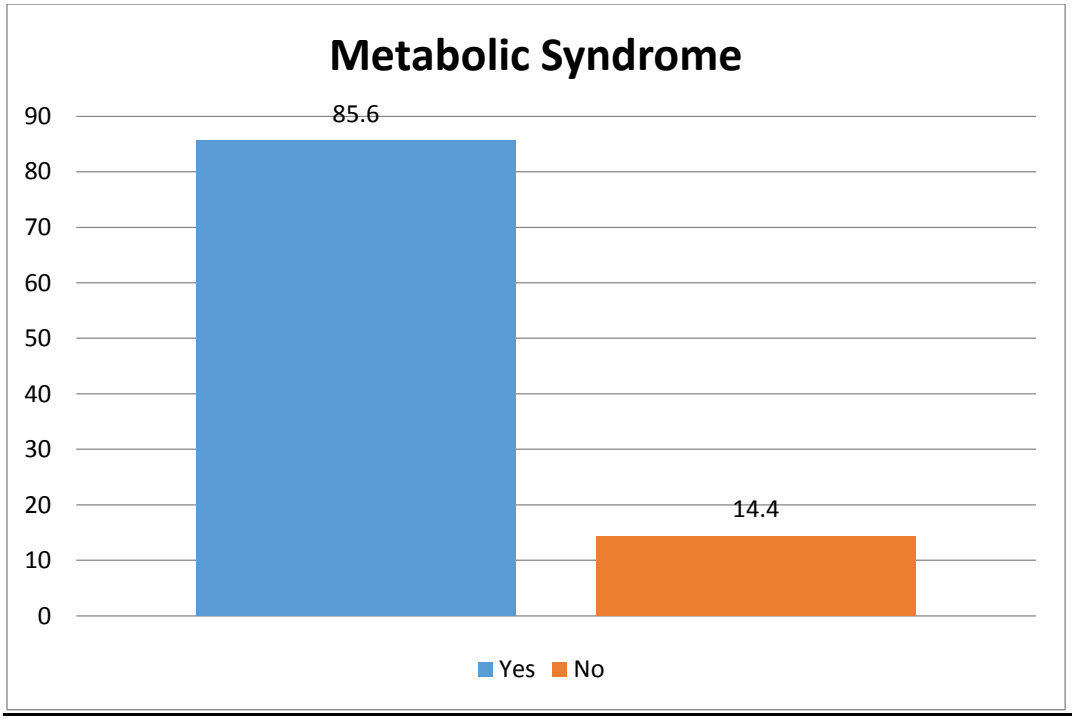


TABLE 19: CRP, FERRITIN, HOMA – IR IN PATIENTS WITH ADVANCED FIBROSIS IN NAFLD

	Mean ± Std.	P Value
CRP (mg/L)	32.40 ± 43.70	0.799
Ferritin (ng/ml)	511.33 ± 640.01	1.000
HOMA – IR	3.53 ± 1.14	0.558

From the above table and graph it was observed that mean CRP was 32.40 ± 43.70 mg/L and mean ferritin was 511.33 ± 640.01 ng/ml. The study also observed that mean HOMO-IR was 3.53 ± 1.14.

FIGURE 21: CRP, FERRITIN, HOMA – IR IN PATIENTS WITH ADVANCED FIBROSIS IN NAFLD

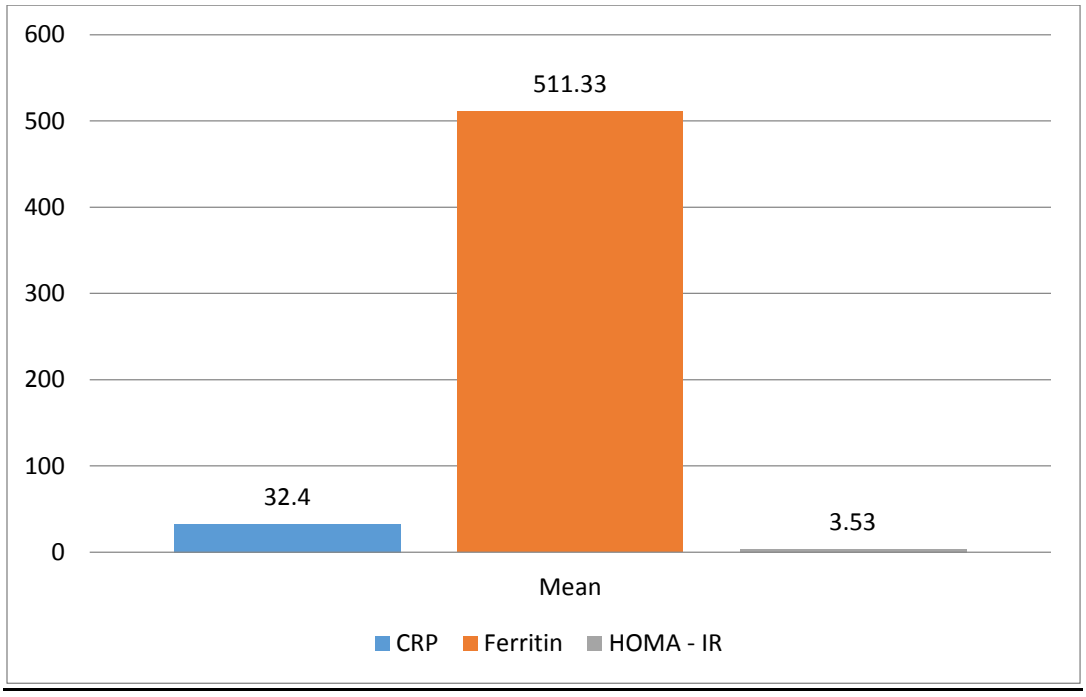


TABLE 20 : HOMA- IR >/= 2.5 IN PATIENTS WITH ADVANCED FIBROSIS IN NAFLD

HOMA – IR (>/=2.5)		
	Frequency	Percent
Yes	73	81.1%
No	17	18.9%

From the above graph it was seen that 81.1% patients had HOMA-IR above the cut off level.

FIGURE 22: HOMA- IR >/= 2.5 IN PATIENTS WITH ADVANCED FIBROSIS IN NAFLD

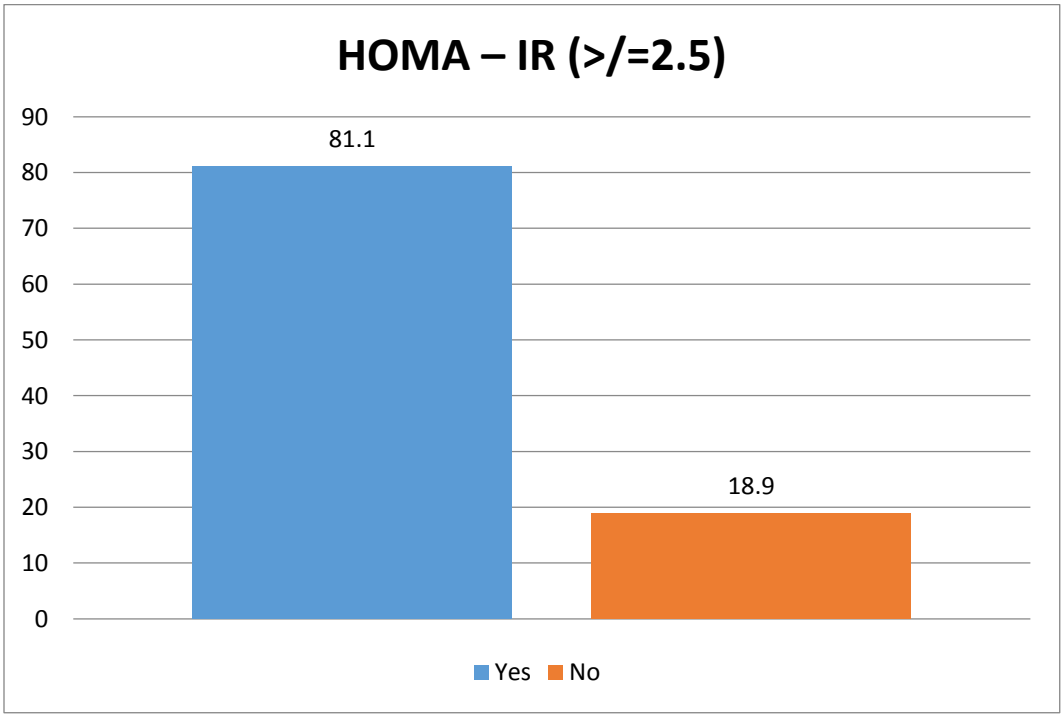


TABLE 21 : METABOLIC SYNDROME TO HOMA-IR (INSULINE RESISITANCE)

Metabolic Syndrome to HOMA – IR(INSULINE RESISITANCE)		p-value
	Mean ± Std.	
Yes	3.84 ± 0.89	0.015
No	1.72 ± 0.68	

From the above table and graph it was observed that mean HOMA-IR in patients with metabolic syndrome was 3.84 ± 0.89 while it was 1.72 ± 0.68 in patients without metabolic syndrome.

FIGURE 23: METABOLIC SYNDROME TO HOMA-IR (INSULINE RESISITANCE)

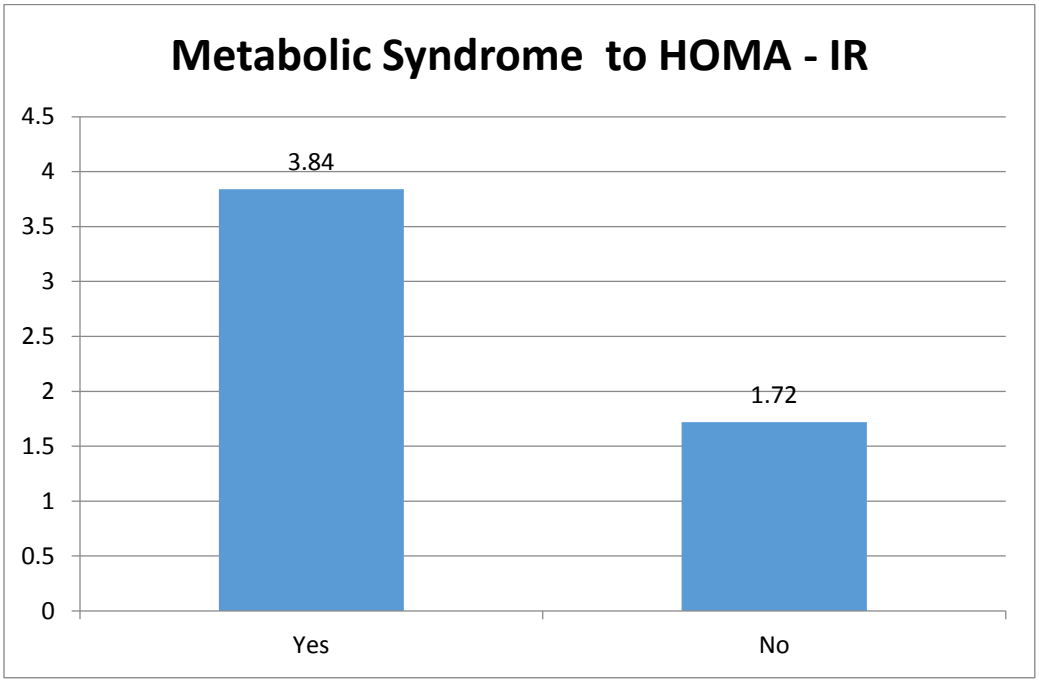


TABLE 22: METABOLIC SYNDROME TO LIPID PROFILE PARAMETERS

Metabolic Syndrome to Lipid Profile parameters(mg/dl)			P-value
	Yes	**No**	
LDL Levels	136.4 ± 31.8	82 ± 15.0	0.012
HDL Levels	31.5 ± 10.2	41.62 ± 8.5	0.052
Total Cholesterol	256.4 ± 47.0	151.92 ± 36.2	0.001
Triglycerides	251.6 ± 52.9	157.85 ± 28.3	0.001

From the above table and graph it was observed that mean LDL levels, HDL levels, total cholesterol and triglycerides was 136.4 ± 31.8 mg/dl, 31.5 ± 10.2 mg/dl, 256.4 ± 47.0 mg/dl, and 251.6 ± 52.9 mg/dl respectively in patients with metabolic syndrome. The study also observed that mean LDL levels, HDL levels, total cholesterol and triglycerides was 82 ± 15.0 mg/dl, 41.62 ± 8.5 mg/dl, 151.92 ± 36.2mg/dl, and 157.85 ± 28.3 mg/dl in patients without metabolic syndrome.

FIGURE 24: METABOLIC SYNDROME TO LIPID PROFILE PARAMETERS

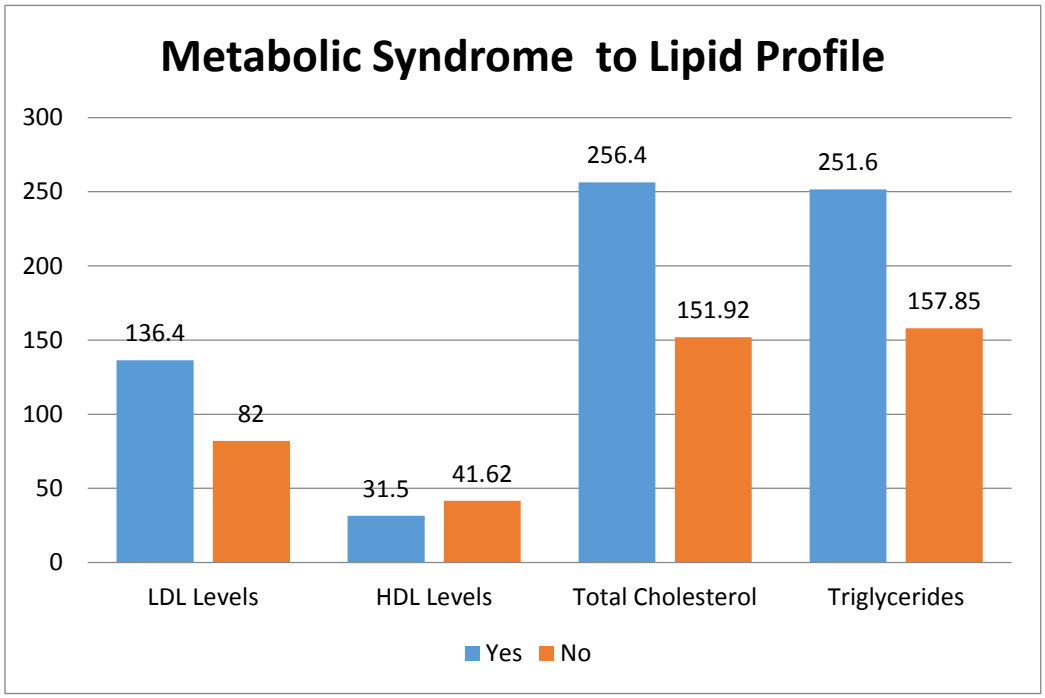


TABLE 23: METABOLIC SYNDROME TO ANTHROPOMETRIC PARAMETER

Metabolic Syndrometo Anthropometric parameters			p-value
	Yes	No	
BMI (kg/m^2)	28.02 ± 3.19	23.72 ± 2.03	0.032
Weight (kg)	90.55 ± 11.31	72.38 ± 8.93	
Waist(cm)	100.36 ± 12.88	89.15 ± 10.27	

From the above table and graph it was observed that mean BMI, weight and waist circumference was 28.02 ± 3.19 kg/m^2, 90.55 ± 11.31 kg, and 100.36 ± 12.88 cm in patients with metabolic syndrome. While, the mean BMI, weight and waist circumference was 23.72 ± 2.03 kg/m^2, 72.38 ± 8.93 kg, and 89.15 ± 10.27 cm in patients without metabolic syndrome.

FIGURE 25: METABOLIC SYNDROME TO ANTHROPOMETRIC PARAMETER

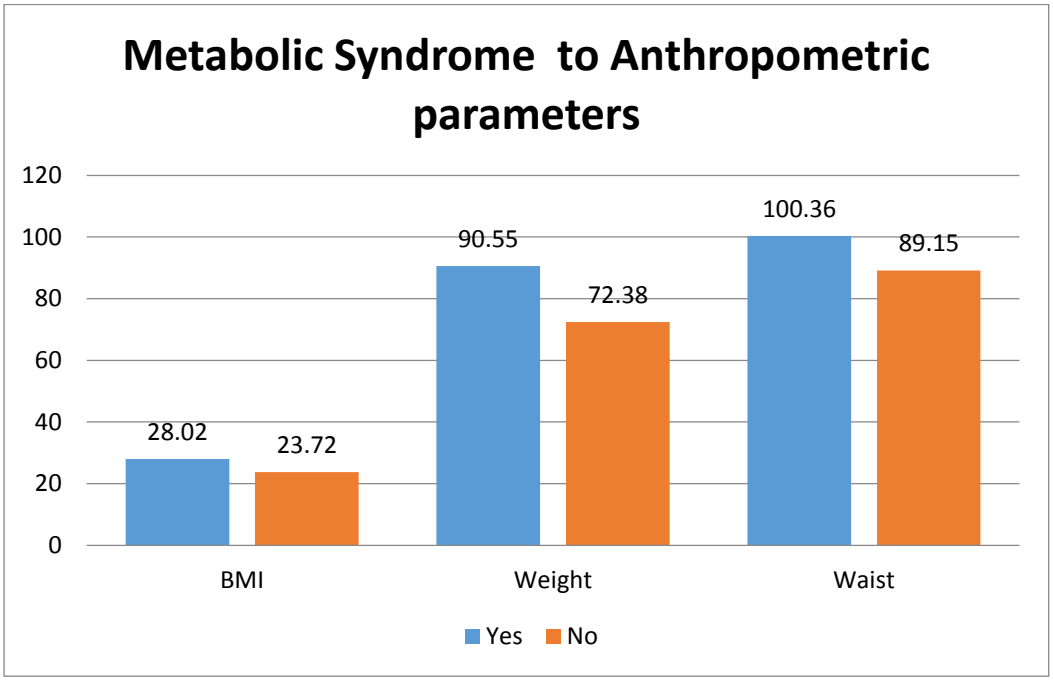


FIGURE 26: ROC CURVE DIABETES MELLITUS TO HOMA - IR

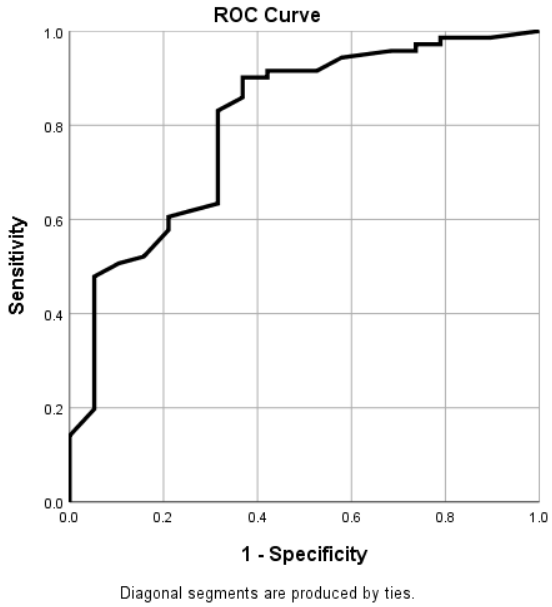


TABLE 24: AUROC FOR DIABETES MELLITUS TO HOMA-IR

Area Under the Curve				
Test Result Variable(s): HOMA - IR				
Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.803	.058	.000	.689	.918
The test result variable(s): HOMA - IR has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.				
a. Under the nonparametric assumption				
b. Null hypothesis: true area = 0.5				

From the above table and graph it was observed that area under the curve (AUC) was 0.803. This finding signified that the AUC was closer to 1 which suggest that diabetic patient having high insulin resistance.

FIGURE 27: ROC Metabolic Syndrome to HOMA – IR

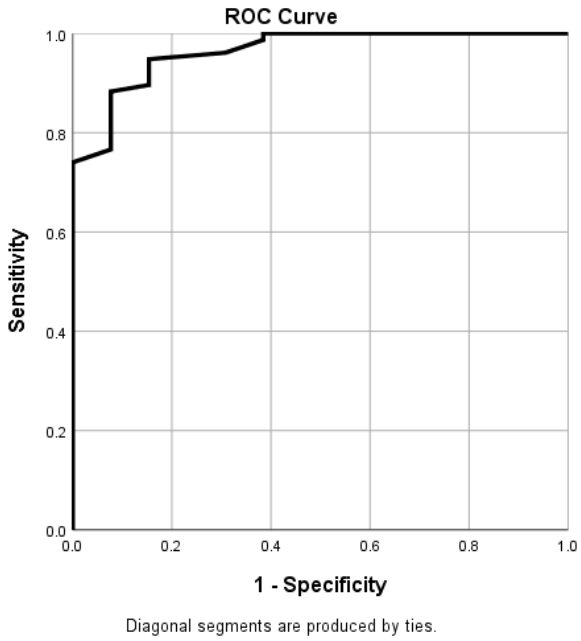


TABLE 25: ROC Metabolic Syndrome to HOMA – IR

Area Under the Curve				
Test Result Variable(s): HOMA - IR				
Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.964	.022	.000	.921	1.000
The test result variable(s): HOMA - IR has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.				
a. Under the nonparametric assumption				
b. Null hypothesis: true area = 0.5				

From the above table and graph it was observed that area under the curve (AUC) was 0.964. This finding signified that the AUC was much closer to 1 which suggest that insuline resisitance is a risk factor for metabolic syndrome.

FIGURE 28: ROC CURVE-Metabolic Syndrome to Lipid Profile

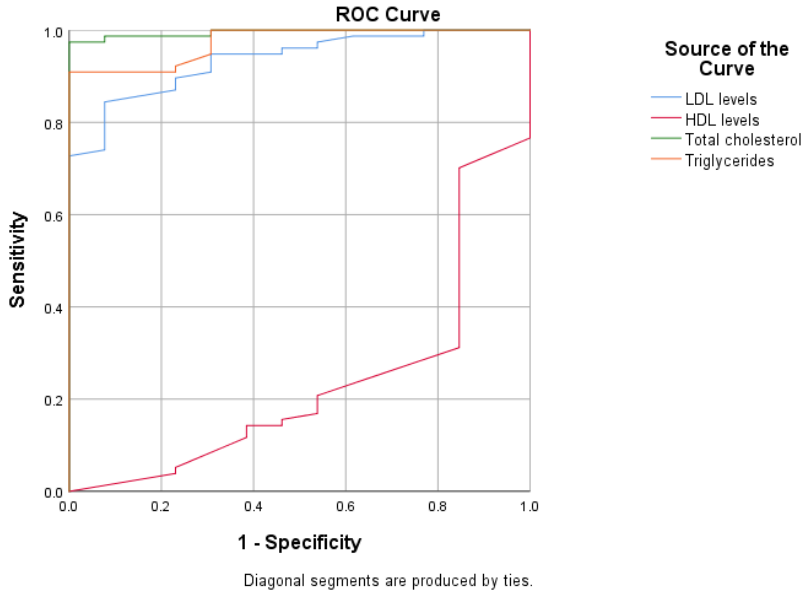


TABLE 26 : AUROC Metabolic Syndrome to Lipid Profile

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
LDL levels	.936	.028	.000	.882	.990
HDL levels	.234	.071	.002	.095	.373
Total cholesterol	.995	.005	.000	.985	1.000
Triglycerides	.974	.015	.000	.945	1.000
The test result variable(s): LDL levels, HDL levels, Triglycerides has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.					
a. Under the nonparametric assumption					
b. Null hypothesis: true area = 0.5					

From the above table and graph it was observed that area under the curve (AUC) for LDL, HDL, TC and triglycerides level was 0.936, 0.234, 0.995

and 0.974 respectively. This finding signified that total cholesterol had the highest AUC, which indicates that dyslipidemias a risk to metabolic syndome.

FIGURE 29: ROC CURVE- Metabolic Syndrome to Anthropometric parameters

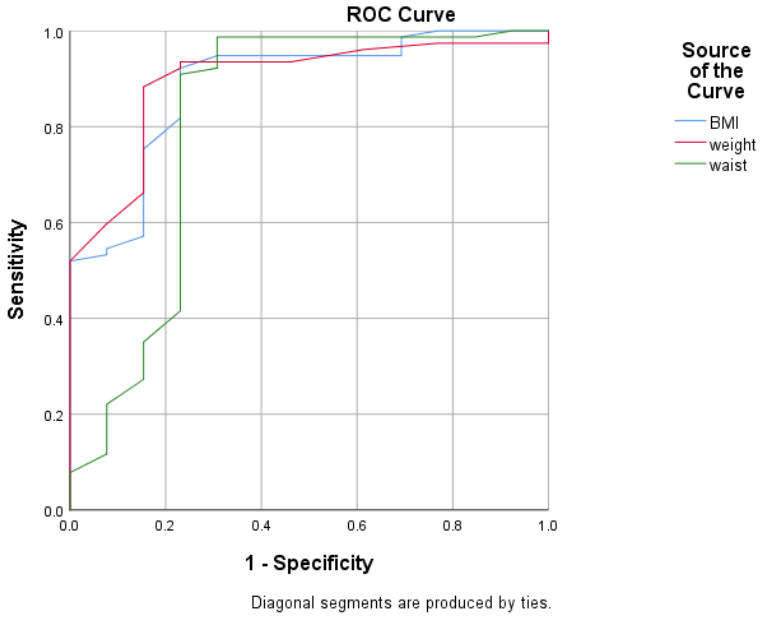


TABLE 27: Metabolic Syndrome to Anthropometric parameters

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error [a]	Asymptotic Sig. [b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
BMI	.888	.048	.000	.794	.982
Weight	.896	.043	.000	.812	.980
Waist	.811	.089	.000	.636	.986
The test result variable(s): BMI, weight, waist has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.					
a. Under the nonparametric assumption					
b. Null hypothesis: true area = 0.5					

From the above table and graph it was observed that area under the curve (AUC) for BMI, weight and waist was 0.888, 0.896 and 0.811 respectively. This finding signified that total body weight had the highest AUC followed

by BMI, which indicates that weight, BMI, waist circumference above refrence range are risk factors of metabolic syndrome.

DISCUSSION

Non-alcoholic fatty liver disease (NAFLD) – ranging from simple fatty liver, through non-alcoholic steatohepatitis (NASH) and fibrosis to NASH-cirrhosis – is highly prevalent, being present in more than 20% of the general population in Europe and North America and higher in the Middle East and South Asia[104]. In most studies, the prevalence is higher in individuals with features of metabolic syndrome including obesity, diabetes, hypertension and an increased waist circumference. Furthermore, several studies have suggested that the presence of these factors also increases the likelihood that people have more advanced forms of NAFLD (fibrosis and NASH)[104].

The incidence of obesity, diabetes, accompanied with NAFLD, has been increasing with the changes of people's life styles[105]. NAFLD is a liver complication often present in diabetic patients. Previous epidemiological report showed that NAFLD was currently the most common cause of chronic liver diseases in countries worldwide[106]. In recent years, studies confirmed that NAFLD is a multisystem disease that affects multiple organs, including hepatic, cardiovascular, and cerebrovascular systems[107]. Therefore, early detection of liver fibrosis can improve the long-term prognosis of patients with NAFLD.

The present study was conducted in a tertiary care hospital in North India which was aimed to see risk factor in patient with advanced fibrosis in non-alcoholic fatty liver disease with mild elevation of transaminases. Although liver biopsy is gold standard test for assessing hepatic fibrosis and steatosis, biopsy procedure can cause certain complications and fatality rate of biopsy is about 0.05%[108]. Also, it is difficult to perform liver biopsy in large population in clinical practice. This study was performed on 90 patients who had advanced fibrosis in NAFLD with mildly raised transaminases to study risk factor. The statistical data hence obtained was compared with previous published literature.

In the present study it was seen that, mean age of the patients was 63.01±11.11 years. The age wise distribution of the patients signified that majority of the patients (35.6%) belonged to age group 56 to 65 years followed by 22.2% patients of age group 66 to 75 years. In a study by Huber et al., it was seen that, mean age of patients with advanced liver fibrosis was 55.0 ± 11.1 years[94]. However, according to Lonardo et al., (2015)[35] epidemiological review, NAFLD has been shown to increase in those who are younger to middle aged with a decline noted after the age of 50-60 years. Similar to our study, In a study conducted by Panyavee Pitisuttithum et al., it was observed that NAFLD was more common in elderly patients with age above 60 years[109].In a similar study conducted by Jessica bazick et al., the mean age group of patients with diabetes and NAFLD was 52.5 ± 10.3 years[110].In present study, 35.6% patients were in age group of 56 to 65 years and only 6.7% patients were < 45 year of age. This shows that patient with increasing age the incidence of advanced fibrosis increase as seen in various above studies.

TABLE 28: MEAN AGE (YEARS)

s.no	Study	Age
1.	Huber et al.,[94]	55.0 ± 11.1 years
2	Jessica bazick et al.,[110]	52.5 ± 10.3 years
3.	Panyavee Pitisuttithum et al.,[109]	Age more than 60 years
4.	Lonardo et al., (2015)[35]	50-60 years
5.	Present study	63.01±11.11 years

The gender wise distribution of patients in our study signified that, study population is dominated by male patients. The study found out that there

were 54.4% males and 45.6% females. Likewise our study, in study by Huber et al., both sex were almost equally represented, with 50.6% being male and 49.4% female.[94] Several studies provide data to suggest a higher prevalence in males while some have proposed the opposite.

The present study has explored the occupation details of the patients. The study found out that majority of the patients (31.1%) were housewife, followed by 17.8% patients who were shopkeeper.

In the present study, there were 78.9% diabetic patients. Extensive review of literature has signified that prevalence of obesity and diabetes mellitus (DM) are gradually increasing[105,111]. It is also known that patient diagnosed with DM can develop a wide range of complications[112]. Diabetes mellitus is not only associated with atherosclerosis, cardiovascular diseases, chronic kidney diseases, and cancer, but also a wide spectrum of chronic liver diseases. DM associated liver disease is thought to be nonalcoholic fatty liver disease (NAFLD) and is ultimately able to lead to liver fibrosis, cirrhosis, and even end-stage liver diseases[113]. Diabetes is one of the component of metabolic syndrome and has been shown to be closely associated with liver fibrosis[114]. However, the relationship between the number of metabolic syndrome components in T2DM patients and liver injury has not been reported[115]. In a study conducted by Targher G et al., the prevalence of NAFLD was 59.67% in diabetes mellitus[116.]A clinical model which predicted advance fibrosis in NAFLD patient with diabetes mellitus was developed by bazick et al. in 2015 which had better accuracy than NAFLD fibrosis score with specificity of 90% and sensitivity of 56.8%[110]. A large study in Italian population with type 2 diabetes reported that 85%had hepatic steatosis and that 70% met the criteria for NAFLD[117]. In our study the p value of diabetes mellitus as a risk factor of advance fibrosis NAFLD was < 0.05 indicating a statistical significance of diabetes as risk factor of advance liver fibrosis in NAFLD in our study.

Glycemic range can be assessed with various methods and one of it is HbA1c. HbA1c, reflecting average glycemic control over the preceding 8-12 weeks and levels with >6.5% as the cutoff points to diagnose diabetes[118]. In our study the mean HbA1c level of patients was 8.94 ±1.60 % which is higher than normal. These findings suggest that the condition of advance fibrosis in patients with non-alcoholic fatty liver disease with mild elevation of transaminases was common in diabetic patients with higher level of HbA1c indicating uncontrolled glycemic status. In a study conducted by Chen C et al., it was seen that patients with upper normal HbA1c levels are likely to develop NAFLD than patients with core normal.[119]In a study conducted by Bae et al., it was also seen that patients with NAFLD had high normal levels of HbA1c and insulin resistance in non diabetic individual.[120]In a study conducted by Feng et al., it was seen that there was increased risk of fibrosis with high HbA1c[121]. In a study done by Jee Hee etal., it was seen that patient with established diabetes , visit to visit HbA1c variability increased the risk of incident of NAFLD.[122]

In our study it was reported that 23.95% patients were on insulin while 76.05% patients were on OHA therapy.

The study found that majority of the patients (38.8%) had diabetes for 1 to 10 years, followed by 26.7% patients who had diabetes for 11 to 20 years. The results signified that there were 11 patients with duration of diabetes greater than 20 years.

In our study statistical significance between HbA1c levels and NAFLD was not found (p value -0.899), since NAFLD is a form of chronic liver disease which develops over months and years, but HbA1c tells glycemic control of only past 12 weeks .

In our study we found out that, there was significant association of diabetes mellitus (p value <0.05) with advance fibrosis with mildly raised transaminases, this is likely as diabetes results in formation of advanced

glycation end products, has high oxidative stress, mitochondrial dysfunction and high level of circulating cytokines results in progression to advanced fibrosis. Patient had a mean HbA1c level of 8.94±1.60% indicating uncontrolled three months glycemic status, with majority of patients having diabetes for minimum 1-10 years and majority of the patient being treated with oral hypoglycemic drugs.

Most of the patients with NAFLD have BMI in either overweight or obese category. High BMI (obesity) is a good predictor of advance liver fibrosis (F3 and F4) [27.] In our study it was reported that mean BMI of the study subjects was 27.39 ± 3.40 kg/m^2.The present study found out that mean weight was 87.92 ± 12.69 kgs. These findings were consistent with the findings of a study by Huber et al., (2022)[94] reported that most participants were overweight (65.4%) with a mean BMI of 27.4 ± 5.02 kg/m^2.In our study we observed that majority of patients who had advanced fibrosis in NAFLD with mildly raised transaminases belonged to obese category, around 80% of the patients were obese. It was also seen that around 12.2% patients were overweight and 7.8% had normal BMI. In a study conducted by Sami Qadari et al., it was seen that in overweight /obese cohort the median BMI was 40.3kg/m^2 , in a Swedish and Italian cohort the it was 28kg/m^2 indicating patients were in overweight category.[123].The study conducted by Sami Qadari et al.,[123] included patients who were already overweight or obese therefore the mean value of BMI was shifted to higher side as compared to our study. In a study conducted by Wong RJ and Aijaz Ahmed, among Asian population average BMI among the fatty liver disease cohort was 25.3± 3.4 kg/m^2 and among non fatty liver disease cohort was 21.8 ±3.0 kg/m^2, this indicates that risk of NAFLD increase with persons having high BMI[124.]. In a study conducted by James B Maurice et al., it was seen that BMI was not associated with increased risk of advance fibrosis, where as type 2 diabetes remained independently associated in multivariate analysis[125.]In a study conducted by Jiwoo lee et

al., it was obsereved that mean BMI was 24.60 ± 2.78 kg/m^2 and the percentage of over weight/obeseity was 70%[126].

In the end to sum up that NAFLD patients having advanced fibrosis have higher BMI, but the statically association (p value .430) was not found in our study likewise study conducted by James B Maurice et al.[125]

TABLE 29: MEAN BMI (kg/m^2)

S.No.	Study	BMI
1.	Huber et al[94]	mean BMI of 27.4 ± 5.02 kg/m^2
2.	Sami Qadari et al.,[123]	in a Swedish and Italian cohort the median BMI was 28kg/m^2
3.	Wong RJ and Aijaz Ahmed,[124]	Mean BMI in fatty liver cohort was 25.3± 3.4kg/m^2
4.	Present	Mean BMI was 27.39 ± 3.40kg/m^2

Waist circumference may be a simple clinical and cost effective tool which can be used as a surrogate marker for NAFLD[127]. Elevated waist circumference correlates with metabolic health and it has also been associated with fatty liver disease. In a study conducted by de Piano et al., it was seen that adolescent with visceral obesity have high risk of developing NAFLD[128]**.**The present study found out that mean waist circumference was 98.74 ± 8.95 cm. From the study it was observed that patient who have advanced fibrosis in NAFLD with mildly raised transaminases have central adiposity. In our study it was found that out of 49 men patients of advanced fibrosis in NAFLD, 77.5% men patient had waist circumference > 94cm which is the cut off point for increased risk of metabolic complication according to WHO. In our study, 41 patients were female out of which each one had waist circumference > 80cm which is the cut off point for increased risk of metabolic complication according to WHO. So from our study it could be seen that patients who had advanced

fibrosis in NAFLD, had cental adiposity with raised waist circumference both for men and women.

Dyslipidemia is one of the most important risk factor that has been associated with advanced fibrosis in NAFLD. Hypertriglyceridemia and low HDL – cholesterol are present in 64% and 30-42% in patients with NAFLD[128]. Atherogenic dyslipidemia characterized by low HDL values and increased triglyceride levels is most common form of dyslipidemias in NAFLD[129.]The present study found out that mean LDL levels of patients was 128.51 ± 35.54 mg/dl with 50% patients having LDL level > 130 mg/dl which was the higher limit of reference age , mean HDL level was 33.00 ± 10.59 mg/dl with around 56.7% patients having HDL levels < 35 mg/dl which was lower limit of reference range, mean total cholesterol was 241.28 ± 58.51 mg/dl with 76.7% patients having total cholesterol above >200 mg/dl which was the higher limit of refrence range, and mean triglycerides was 238.08 ± 60.01 mg/dl with 71.1% patients having triglycerides > 200 mg/dl which was the higher limit of reference range. In the study conducted by Mendez-sanchez et al., it was seen that in the patient who had advanced fibrosis in NAFLD, the mean LDL was 112.5 ± 23.9 mg/dl, mean HDL was 38.2 ± 12 mg/dl, mean total cholesterol was 189 ± 51.3 mg/dl and mean triglycerides were 168.1 ± 58.6 mg/dl, indicating patient having dyslipidemia in advanced fibrosis[130.]. Similar findings were reported by Huber et al., (2022). Huber et al.,[94] reported that dyslipidemia was present in 34.6%, with a mean LDL of 139.0 ± 35.5 mg/dL, mean HDL of 57.3 ± 15.6 mg/dL, and mean total cholesterol of 221.0 ± 40.8 mg/dL. In a study conducted by Ganjooei NA et al., it was observed that patients who had fibrosis in NAFLD had mean LDL cholesterol of 106.9 ± 30mg/dl , mean cholesterol was 182.5 ± 40 mg/dl[131.]In another study conducted by Julian, M.T. Et al., it was seen that patients with liver fibrosis had a mean LDL cholesterol 110 ± 38 mg/dl , mean HDL levels of 43 ± 10 mg/dl, mean total cholesterol of 193 ± 39

mg/dl, mean triglycerides of 235 ± 142 mg/dl[132].In another study conducted by Souza et al., condition of hypercholesterolemia and hypertriglyceridemia, were reported to around 80% in patients of NAFLD[133.] In a study conducted by Gupta et al., the mean cholesterol was higher in patients with moderate NASH as compared to that of mild NASH[134].

TABLE 30. MEAN LIPID PROFILE PARAMETERS

S.NO.	STUDY	MEAN LDL	MEAN HDL	MEAN TOTAL CHOLESTEROL
1.	Mendez-sanchez et al.[130]	112.5 ± 23.9 mg/dl	38.2 ± 12 mg/dl	189 ± 51.3 mg/dl
2.	Huber et al.,[94]	139.0±35.5 mg/dl	57.3 ± 15.6 mg/dl	221.0 ± 40.8 mg/dl
4.	Julian, M.T. Et al[132]	110 ± 38 mg/dl	43 ± 10 mg/dl	193 ± 39 mg/dl
5.	Present	128.51 ± 35.54 mg/dl	33.00 ± 10.59 mg/dl	241.28 ± 58.51 mg/dl

In our study it was also observed that majority of patients with advanced fibrosis in NAFLD had Hypertriglyceridemia and low HDL level as seen in previous studies. In present study likewise other studies significant association was found between advance fibrosis and high total cholesterol levels with p value of 0.05. In our study the significance of HDL , LDL and triglycerides were not found, one possible reason could be us of statins among the patients.

Transaminitis is a good indicator of hepatocellular injury. In our study the result signified that mean AST levels was 56.96 ± 11.47 u/l, and ALT levels was 61.64 ± 12.19 u/l. Similar findings were reported by Huber et al., (2022). Huber et al., reported that elevated liver enzymes were detected in almost a fifth of all participants and most frequently seen for increased ALT levels (19.9%), whereas increased AST levels were present in 12.8%.In a study conducted by Thong et al., it was observed that mean AST levels were 57 ± 34 u/l and mean ALT levels were 63 ± 32 u/l which where to similar to our study[95.]In our study it was observed that ALT levels were slightly more raised as compared to AST levels. In a study conducted by kunde et al, with reference cut of value of 43 u/l for ALT it was seen that elevated ALT levels in 8.6% of their study population[135.] In our study we took patients who already had mildly elevated AST and ALT levels therefore AST and ALT levels were raised as it was the inclusion criteria therefore all patients had elevated AST and ALT levels.

The study found out that AST/ALT ratio was 0.95 ± 0.2. In a study conducted by sattar N et al.,it was seen that patients with advance disease in NAFLD had AST/Alt ratio >0.8 and patients with alcoholic liver disease have AST/ALT ratio > 1.5.[136]

Thrombocytopenia represent a marked feature of advanced liver disease, but its prevalence and features and significance in NAFLD are not very clear and this is likely due to low thrombopoietin produced by fibrotic liver[137.]. The results in our study signified that mean platelet count was 96755.56 ± 43945.40 ul^{-1} in patients advanced fibrosis in NAFLD with mildly range transaminases.

Metabolic syndrome includes various metabolic disorders such as abdominal obesity, hypertension, dyslipidemias and impaired glycaemia[138.] Insulin resistance is an important component of metabolic

syndrome and insulin resistance has role in pathogenesis of both metabolic syndrome and NAFLD. In the present study 85.6% patients were identified with metabolic syndrome. In a study conducted by Gangireddy et al., the relationship between metabolic syndrome and its component with hepatic fibrosis and steatosis was investigated and which showed that patients with metabolic syndrome have three times high risk of developing hepatic fibrosis than patients without metabolic syndrome[139].In the study conducted with korean health checkup examinees there was high prevalence rate of significant liver fibrosis in subjects with metabolic syndrome[140.] In a study conducted by M Prashanth et al., the presence of severity and fibrosis in NAFLD with number of component of metabolic syndrome was seen and it was observed that prevelance of NASH increase from 54% to 83% when there was increase in component of metabolic syndrome from three to five[102.] In a study conducted by Tarik Kani H et al., it was seen that 77.1 % patients who had advanced fibrosis in NAFLD were having metabolic syndrome[141]. In a study conducted by Hamagushi et al., (2005)[142] it was found that the Metabolic syndrome is a strong risk factor for nonalcoholic fatty liver disease. Participants with the Metabolic syndrome had a 4 to 11 times higher risk for developing advanced fibrosis in NAFLD.

The prevalence of metabolic syndrome reported in our study was higher than that of previous studies. Huber et al., (2022)[94] in their study reported that the prevalence of metabolic syndrome was 30.5%, with a prevalence of 38.7% in men and 22.2% in women. This was likely because majority of the patient in our studies had diabetes with uncontrolled glycemic status increasing the risk of insulin resistance thus leading to increased prevalence of metabolic syndrome. Likewise our study also founded that metabolic syndrome as risk factor of advanced fibrosis in NAFLD with mildly raised transaminases with p value of <0.05.

In our study, Patients who had metabolic syndrome had mean HOMA –IR value of 3.84 with standard deviation of 0.89 and patients who didn't had metabolic syndrome had mean HOMA- IR value of 1.72 with standard deviation of 0.68, showing statistical significance between metabolic syndrome with HOMA-IR with p value of 0.015. In our study, area under the roc curve (AUROC) when compared for metabolic syndrome to HOMA-IR was 0.964 since the AUROC was close to 1 suggest that patients who have higher value of HOMA-IR have more chances of metabolic syndrome.

Comparison was also made between patients of who had metabolic syndrome and patients who didn't have metabolic syndrome with dyslipidemias (lipid profile parameters). The study found out that mean LDL levels,mean HDL levels,mean total cholesterol and mean triglycerides was 136.4 ± 31.8 mg/dl, 31.5 ± 10.2 mg/dl, 256.4 ± 47.0 mg/dl, and 251.6 ± 52.9 mg/dl respectively in patients with metabolic syndrome while mean LDL levels,mean HDL levels,mean total cholesterol and mean triglycerides was 82 ± 15.0 mg/dl, 41.62 ± 8.5 mg/dl, 151.92 ± 36.2 mg/dl, and 157.85 ± 28.3 mg/dl in patients without metabolic syndrome. The study reported a statistically significant association between metabolic syndrome and lipid profile parameters of patients (p-value<0.05). LDL, total cholesterol, and triglycerides was significantly higher in patients with metabolic syndrome ($p<0.05$). In our study AUROC for LDL, HDL, TC and triglycerides level was 0.936, 0.234, 0.995 and 0.974 respectively. This finding signified that total cholesterol had the highest AUC, which indicates that it has the highest area under the curve and is the risk factor for metabolic syndrome.

Comparison was also made between patients had metabolic syndrome and patients who didn't have metabolic syndrome with obesity (anthropometric parameters). In patients with metabolic syndrome the mean BMI was 28.02 ± 3.19 kg/m^2 belonging to obese category according to Asian BMI classification, where as it ws 23.72 ± 2.03 kg/m^2 belonging to

overweight category. The study found out that BMI was significantly higher in patients with metabolic syndrome ($p<0.05$).The present study found out that there was a significant association between metabolic syndrome and obesity (anthropometric parameters ($p=0.032$)). In our study AUROC for BMI, weight and waist was 0.888, 0.896 and 0.811 respectively. This finding signified that total body weight had the highest AUROC followed by BMI, which indicates that weight has the highest area under the curve and is the strongest risk factor metabolic syndrome.

Insulin resistance plays important role in progression to advanced fibrosis in NAFLD. In our study we saw the homeostasis model assessment of insulin resistance values in patients with advanced fibrosis in NAFLD. In our study mean HOMA –IR was 3.53 ± 1.14 which was more than cut off of 2.5 taken as indicator of IR. In a study Fujii et al., (2019)[143] it was seen that median HOMA-IR of the patients was 2.88. This study also reported that along with age and dyslipidemia, HOMA-IR was also an independent predictor of advanced fibrosis in patients with non diabetic non-alcoholic fatty liver disease. Likewise, our study Singh et al., (2015)[78] in their study reported higher level of HOMA-IR in NAFLD patients. The mean HOMA-IR reported was 2.53 ± 2.57 in patients with NAFLD. In the study conducted by Calpod, O.P.; et al., it was seen that mean HOMA –IR in patients with advanced fibrosis in NAFLD was 3.38 ± 0.85 which is similar to our study[144].

In our study mean CRP values and ferritin values were found statistically insignificant with p value >0.05. Similarly in a Romanian study CRP was useful in predicting NASH, but was not a marker of advanced fibrosis in NAFLD[145].

In line with findings of our study, Zhao et al., (2018)[115] reported that older age, high BMI, smoking, and low PLT levels are independent risk factors for liver fibrosis in patients with diabetes. Consistently, older age, low PLT

level high BMI have also been reported to be associated with liver fibrosis[146]. A study in South Korea explored the relationship between liver enzymes and NAFLD. The results showed that NAFLD was closely related to enzyme levels, and it was also positively correlated with diabetes[147].

Based on our results, patients with metabolic syndrome, diabetes mellitus and dyslipidemias should be screened for advance fibrosis, especially overweight patients with high level of HOMA-IR, LDL, total cholesterol and triglycerides. Timely interventions should be taken into consideration for these patients.

In line with the findings of our study, previous studies have reported that age older than 45 years, presence of obesity, and type 2 diabetes mellitus or other risk factors of metabolic syndrome is associated with advanced liver fibrosis[82,148].

Our study has some limitations. The sample size is relatively small and patients were enrolled in a single center. A multicenter study is warranted to validate the findings of our study.

SUMMARY & CONCLUSION

Summary

The summary of the major findings of the study are as follows:

- The present study aimed to identify risk factors in patients with advanced fibrosis in non-alcoholic fatty liver disease (NAFLD) with mild elevation of transaminases.
- The study was performed on 90 patients and was found out that mean age of the patients of advanced fibrosisi was 63.01±11.11 years.
- The age wise distribution of the patients signified that majority of the patients (35.6%) belongs to age group 56 to 65 years followed by 22.2% patients of age group 66 to 75 years.
- The gender wise distribution of the patients signified that there was 54.4% males and 45.6% females.
- The study found significant statistical association between advanced fibrosis in NAFLD with mildly elevated transaminases and diabetes mellitus.
- The study found out diabetes in 78.9% patients. The results signified that majority of the patients (38.8%) have diabetes for 1 to 10 years, followed by 26.7% patients who had diabetes for 11 to 20 years.
- The study found out mean HbA1c level of patients was 8.94±1.60%.
- The study found out 23.95% patients were on insulin while 76.05% patients were on OHA therapy.
- The mean BMI of the study subjects was 27.39 ± 3.40 kg/$m^2$and most participants were obese.
- The mean weight was 87.92 ± 12.69 kgs and mean waist circumference was 98.74 ± 8.95 cm. Around 77.5% men had a

waist circumference of >94cm which was the reference for metabolic complication by WHO in men and all women had waist circumference of >80cm which was the reference for metabolic complication by WHO in women.

- Mean LDL levels were 128.51 ± 35.54 mg/dl, HDL levels were 33.00 ± 10.59 mg/dl, Total Cholesterol was 241.28 ± 58.51mg/dl, and triglycerides were 238.08 ± 60.01mg/dl.
- The study found out that 85.6% of patients were identified with metabolic syndrome.
- The mean platelet count was 96755.56 ± 43945.40, mean AST levels were 56.96 ± 11.47 U/l, and ALT levels were 61.64 ± 12.19 U/L. The AST/ALT Ratio was 0.95 ± 0.2.
- The study found out significant association between adbvanced fibrosis in NAFLD and diabetes mellitus, metabolic syndrome, total cholesterol.
- The study found out significant association between metabolic syndrome and BMI, HOMA-IR, LDL, total cholesterol, triglycerides, lipid profile parameters of patients(dyslipidemias) ($p<0.05$).

Conclusion

The present study aimed to identify risk factors in patients with advanced fibrosis in non-alcoholic fatty liver disease (NAFLD) with mild elevation of transaminases. The study was performed on 90 patients.

The study population consisted of 90 patients with a mean age of 63.01±11.11 years, and majority of the patients belonged to the upper-middle age group. This was similar to various study cited in the result., so it can said that increasing age is a demographic risk factor for advance fibrosis in NAFLD. The study population was dominated by male patients (54.4%).

The study found that 78.9% of the patients had diabetes with a p value of <0.05 indicating that diabetes is a risk factor for advanced fibrosis in NAFLD, with the mean HbA1c level of 8.94±1.60% it showed that most of patient had a poor three month glycemic control. The significant association between HbA1c with advance fibrosis in NAFLD was not found as HbA1c levels tell us the glycaemic controls of only last three months. Out of total diabetic patients 23.95% of the patients were on insulin therapy while 76.05% were on OHA therapy.

The mean BMI of the study subjects was 27.39 ± 3.40 kg/m^2, with a mean weight of 87.92 ± 12.69 kgs and mean waist circumference of 98.74 ± 8.95 cm. The significant association between anthropometric data was not found (p value >0.05) it could be because in our study it included on weight and waist circumference which is affected by various factors like dietary factors, sedentary life style and most of patients were on OHA which could lead to weight loss.

The study also reported the mean lipid profile parameters, including mean, LDL levels 128.51 ± 35.54 mg/dl, HDL levels 33.00 ± 10.59 mg/dl, total cholesterol 241.28 ± 58.51 mg/dl, and triglycerides 238.08 ± 60.01 mg/dl significant association was only found to be with total cholesterol with p value of <0.05 and not with LDL, Triglycerides and HDL levels this could be because of use of statins among them.

In our study significant association was also found between advanced fibrosis in NAFLD with mildly raised transaminases and metabolic syndrome with p value <0.05. 85.6% of the patients were identified with metabolic syndrome, which was associated with a higher HOMA-IR (3.84 ± 0.89) compared to patients without metabolic syndrome (1.72 ± 0.68). The study also found a significant association between metabolic syndrome and the obesity (anthropometric measures (p=0.032)) and dyslipidemia (lipid profile parameters (p-value<0.05))

and HOMA-IR (p – value <0.05). The mean HOMA- IR reported in our study was 3.53 ± 1.14.

In conclusion, the study reported that upper-middle age group, male gender, diabetes, metabolic syndrome and abnormal lipid profile are the risk factors in patients with advanced fibrosis in NAFLD with mild elevation of transaminases. However, a larger, multi-center, and controlled randomized study is necessary to strengthen the validity of our findings.

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PROFORMA

Sr. No

NAME MRD NO.

AGE/ SEX:

FATHER'S NAME

ADDRESS

OCCUPATION:

DATE OF ADMISSION

DATE OF DISCHARGE

RISK FACTORS –

1 Diabetes mellitus

a)Duration

b)Hba1c levels

c)On diet /drug therapy

2 lipid profile

a)LDL levels

b)HDL levels

c)Total cholesterol

d)Triglycerides

3 Anthropometric

a)BMI

b)weight

c)waist

Signature of Candidate

Signature of Supervisor

4 Lab Parameter

a) Platelet count

b) AST levels

c) ALT levels

d) AST/ALT Ratio

5 Metabolic syndrome

Yes / No

6 CRP

7 Ferritin

8 HOMA - IR

Signature of Candidate

Signature of Supervisor

						Diabetes mellitus			lipid profile							
Sr. No	MRD NO	AGE/ SEX	OCCUPATION	DATE OF ADMISSION	DATE OF DISCHARGE	Duration	Hba1c levels (%)	On diet /drug therapy	LDL levels (mg/dl)	Ldl levels >130mg/dl	HDL levels (mg/dl)	HDl<35 mg/dl	Total cholesterol (mg/dl)	Total cholesterol >200mg/dl	Triglycerides(mg/dl)	Triglycerides >200mg/dl
1	1112025	60/male	Business	22-05-2021	01-06-2021	11 year	8.4	ON OHA	160	y	33	y	295	y	268	y
2	375369	63/male	Farmer	04-06-2021	18-06-2021	NON DIABETIC	-	-	106	n	30	y	190	n	200	n
3	301874	50/female	labourer	08-05-2021	10-08-2021	NON DIABETIC	-	-	188	y	30	y	236	y	230	y
4	934660	61/male	Farmer	15-05-2021	19-05-2021	4 year	6.9	ON OHA	140	y	32	y	259	y	215	y
5	930484	48/male	Business	18-05-2021	25-05-2021	8 year	8.1	ON OHA	125	n	48	n	200	n	233	y
6	999410	50/male	Business	10-10-2021	15-10-2021	NON DIABETIC	-	-	88	n	45	n	102	n	145	n
7	1077158	60/female	Housewife	10-06-2021	14-06-2021	NON DIABETIC	-	-	75	n	50	n	270	y	254	y
8	739845	64/male	Shopkeeper	14-06-2021	25-06-2021	15 year	9	ON OHA	148	y	18	y	232	y	221	y
9	1123279	68/female	Housewife	16-06-2021	23-06-2021	13 year	6.6	ON OHA	153	y	26	y	292	y	182	n
10	1085169	81/female	Dependent	13-04-2021	21-04-2021	NON DIABETC	-	-	90	n	35	n	244	y	267	y
11	1098571	48/female	Housewife	29-04-2021	09-05-2021	6 year	13	ON OHA	177	y	10	y	311	y	205	y
12	147870	69/female	Dependent	14-06-2021	21-06-2021	10 year	12.2	ON Insulin	165	y	12	y	250	y	303	y
13	91820	48/female	house wife	10-09-2021	15-09-2021	9 year	9.2	ON Insulin	93	n	48	n	188	n	131	n
14	1110958	70/male	Farmer	19-05-2021	29-05-2021	10 year	7	ON Insulin	181	y	18	y	395	y	475	y
15	1127084	76/male	Shopkeeper	24-06-2021	30-06-2021	1 year	7.1	ON OHA	65	n	25	y	177	n	196	n
16	1129575	49/male	Business	29-06-2021	03-07-2021	10 year	12.5	ON Insulin	133	y	25	y	299	y	190	n
17	984199	60/male	labourer	06-08-2021	09-08-2021	4 year	13.4	ON OHA	146	y	40	n	254	y	255	y
18	1212056	60/male	Dependent	23-11-2021	28-11-2021	6months	6.9	ON OHA	160	y	46	n	250	y	290	y
19	1247664	62/mlae	Dependent	02-02-2022	06-02-2022	10 year	8	ON OHA	130	n	20	y	268	y	238	y
20	497666	47/male	Farmer	10-11-2021	03-11-2021	4 year	9.2	ON OHA	157	y	28	y	330	y	212	y
21	122817	52/male	Business	31-12-2021	04-01-2022	NON DIABETIC	-	-	115	n	28	y	266	y	202	y
22	1250361	76/female	Housewife	08-01-2022	12-01-2022	10 year	8	ON OHA	190	y	50	n	332	y	320	y
23	1251031	56/female	Housewife	11-01-2022	13-01-2022	6.5 year	10	ON Insulin	75	n	50	n	101	n	138	n
24	1250550	65/female	Dependant	13-01-2022	17-01-2022	14 year	9.8	ON Insulin	147	y	20	y	296	y	292	y
25	1249477	52/male	ernment emplo	06-02-2022	11-02-2022	7 year	7.8	ON OHA	111	n	40	n	172	n	151	n
26	1249688	40/female	Dependant	10-02-2022	13-02-2022	NON DIABETIC	-	-	88	n	48	n	133	n	190	n
27	1234068	44/male	Self Employed	10-02-2022	14-02-2022	10 year	9.1	ON OHA	148	y	40	n	245	y	188	n
28	6961	61/female	Dependant	31-01-2022	16-02-2022	12 year	11.1	ON Insulin	144	y	22	y	220	y	215	y
29	1249148	89/male	Shopkeeper	05-02-2022	10-02-2022	24 year	12	ON Insulin	139	y	40	n	223	y	342	y
30	429390	64/female	Dependent	13-02-2022	20-02-2022	NON DIABETIC	-	-	94	n	30	y	282	y	301	y
31	124209	78/female	house wife	08-02-2022	14-02-2022	NON DIABETIC	-	-	79	n	44	n	222	y	259	y
32	921049	64/female	Dependent	11-02-2022	20-02-2022	10 yaer	7.9	ON OHA	167	y	50	n	307	y	211	y
33	1134014	61/female	Farmer	08-07-2021	12-07-2021	14 year	7.3	ON OHA	150	y	49	n	249	y	278	y
34	1129568	55/female	Housewife	29-06-2021	12-07-2021	8 year	8.2	ON OHA	72	n	50	n	130	n	168	n
35	1136497	71/male	Shopkeeper	13-07-2021	20-07-2021	NON DIABETIC	-	-	102	n	28	y	348	y	299	y
36	1136555	44/female	house wife	14-07-2021	20-07-2021	11 year	9.1	ON Insulin	132	y	48	n	200	n	176	n
37	1128947	52/male	bussiness	28-06-2021	01-07-2021	8 year	8.2	ON OHA	143	y	38	n	366	y	199	n
38	1138757	35/ male	bussiness	17-07-2021	23-07-2021	5 year	9.3	ON insulin	180	y	37	n	209	y	288	y

		RISK FACTORS																
		BMI - kg/m2					waist circumfrence (cm)			Lab Parameter							HOMA - IR	
Sr. No	MRD NO	BMI (kg/m2)	normal	over weight (23-24.9)kg/m2	obese>/=25 kg/m2	weight (kg)	waist circumfrence (cm)	Men >94cm	female >80cm	Platelet count (/UL)	AST levels (U/L)	ALT levels (U/L)	AST/ALT Ratio	Metabolic syndrome	CRP (mg/L)	Ferritin (ng/ml)	absolute value	>/=2.5
1	1112025	28	-	-	y	90kgs	113cm	y	-	168000	42	61	0.83	yes	6.37	159.9	5	y
2	375369	22.8	y	-	-	70kg	101cm	y	-	93000	78	49	1.59	yes	68	330	1.78	n
3	301874	30	-	-	y	85kgs	115cm	-	y	273000	66	44	1.5	yes	16	290	2	n
4	934660	32.4	-	-	y	100kgs	120cm	y	-	125000	55	48	1.14	yes	300	2600	6.78	y
5	930484	33	-	-	y	96kgs	106cm	y	-	60000	55	55	1	yes	62	150	3.2	y
6	999410	22	y	-	-	89kgs	84cm	N	-	90000	62	62	1	NO	10	82	1.6	n
7	1077158	31.8	-	-	y	90kgs	100cm	-	y	120000	46	44	0.95	yes	15	25	2	n
8	739845	32	-	-	y	82kgs	112cm	y	-	112000	75	41	1.8	yes	13	74	3.4	y
9	1123279	22.3	y	-	-	55kgs	88cm	-	y	100000	70	44	1.59	yes	8.7	91	3.7	y
10	1085169	38	-	-	y	110kgs	120cm	-	y	307000	50	50	1	yes	48	200	1.9	n
11	1098571	41.3	-	-	y	93kgs	101cm	-	y	92000	45	55	0.8	yes	25	1397	4.8	y
12	147870	35	-	-	y	96kgs	122cm	-	y	80000	42	42	1	yes	0.69	30.8	3.92	y
13	91820	23.1	-	y	-	68kgs	83cm	-	y	100000	60	74	0.8	No	4	99	1.7	n
14	1110958	30	-	-	y	92kgs	110cm	y	-	60000	41	77	0.53	yes	141	1385	2.79	y
15	1127084	23.5	-	y	-	70kgs	110cm	y	-	111000	68	69	0.9	No	15	720	1.5	n
16	1129575	29	-	-	y	85kgs	107cm	y	-	80000	74	74	1	yes	24	27	4.12	y
17	984199	31.5	-	-	y	103kg	99cm	y	-	56000	49	59	0.83	yes	3	380	5.5	y
18	1212056	27.6	-	-	y	80kgs	101cm	y	-	98000	42	42	1	yes	26	80	3.2	y
19	1247664	30	-	-	y	101kgs	106cm	y	-	90000	52	55	0.945	yes	200	2680	4	y
20	497666	32.3	-	-	y	96kgs	94cm	n	-	60000	68	68	1	yes	92	296	3.2	y
21	122817	27	-	-	y	90kgs	101cm	y	-	28000	62	75	0.82	yes	8	500	1.8	n
22	1250361	24	-	y	-	68kgs	95cm	-	y	92000	48	76	0.63	yes	71	286	3.8	y
23	1251031	27.5	-	-	y	72kgs	103cm	-	y	82000	47	47	1	No	101	321	3.3	y
24	1250550	32	-	-	y	108kgs	100cm	-	y	72000	42	61	0.68	yes	92	632	3.9	y
25	1249477	24	-	y	-	60kgs	85cm	n	-	110000	45	45	1	No	90	931	1.9	n
26	1249688	23.4	-	y	-	66kgs	83cm	-	y	165000	41	80	0.512	No	56	120	1.2	n
27	1234068	22.1	y	-	-	56kgs	88cm	n	-	60000	50	45	1.11	yes	60	234	3.9	y
28	6961	31	-	-	y	95kgs	105cm	-	y	27000	56	80	0.7	yes	73	720	4	y
29	1249148	30.1	-	-	y	92kgs	102cm	y	-	100000	74	36	2.05	yes	10	112	4.12	y
30	429390	26	-	-	y	83kgs	99cm	-	y	73000	48	50	0.96	yes	92	3926	3	y
31	124209	27	-	-	y	88kgs	103cm	-	y	92000	56	56	1	yes	48	826	1.8	n
32	921049	28	-	-	y	80kgs	99cm	-	y	150000	58	62	0.9	yes	4	101	3.3	y
33	1134014	25.1	-	-	y	90kgs	97cm	-	y	175000	78	78	1	yes	12	180	3.6	y
34	1129568	21.2	y	-	-	70kgs	81cm	-	y	130000	68	68	1	No	0.8	232	1.8	n
35	1136497	28.1	-	-	y	101kgs	108cm	y	-	70000	48	59	0.81	yes	57	329	3.91	y
36	1136555	26	-	-	y	83kgs	103cm	-	y	40,000	77	77	1	yes	32	292	4.12	y
37	1128947	31	-	-	y	102kgs	110cm	y	-	1,70,000	63	79	0.79	yes	80	621	4.18	y
38	1138757	28.5	-	-	y	98kgs	104cm	y	-	72,000	55	55	1	yes	29	171	3.86	y

						Diabetes mellitus			lipid profile							
Sr. No	MRD NO	AGE/ SEX	OCCUPATION	DATE OF ADMISSION	DATE OF DISCHARGE	Duration	Hba1c levels (%)	On diet /drug therapy	LDL levels (mg/dl)	Ldl levels >130mg/dl	HDL levels (mg/dl)	HDl<35 mg/dl	Total cholesterol (mg/dl)	Total cholesterol >200mg/dl	Triglycerides(mg/dl)	Triglycerides >200mg/dl
39	1140441	65/female	house wife	21-07-2021	10-08-2021	NON DIABETIC	-	-	98	n	50	n	192	n	145	n
40	1150300	55/male	Farmer	07-08-2021	12-08-2021	5 year	7.9	ON oha	81	n	40	n	188	n	196	n
41	914654	61/female	house wife	18-08-2021	20-08-2021	10 year	10.2	ON insulin	130	n	48	n	332	y	308	y
42	1150555	75/female	house wife	22-08-2021	26-08-2021	20 years	7.7	ON OHA	61	n	42	n	171	n	149	n
43	1161920	70/Male	farmer	26-08-2021	30-08-2021	NON DIABETIC	-	-	94	n	42	n	240	y	220	y
44	1162688	62/Male	Shopkeeper	27-08-2021	01-09-2021	NON DIABETIC	-	-	70	n	48	n	299	y	300	y
45	1160398	47/Male	Shopkeeper	24-08-2021	28-08-2021	4 year	7.1	ON OHA	67	n	38	n	188	n	192	n
46	1161193	70/female	ernment emplo	25-08-2021	29-08-2021	22 yaer	8.1	ON OHA	115	n	18	y	268	y	344	y
47	1140612	64/female	Dependant	06-09-2021	10-09-2021	10 year	8.8	ON OHA	190	y	22	y	245	y	233	y
48	1176027	58/Male	Self Employed	18-09-2021	22-09-2021	12 year	8.1	ON OHA	140	y	32	y	255	y	200	n
49	1172979	65/Male	business	14-09-2021	20-09-2021	12 year	10.8	ON OHA	110	n	41	n	352	y	272	y
50	1180763	63/male	Self employed	27-09-2021	11-10-2021	7 year	11.1	On insulin	142	y	30	y	198	n	210	y
51	853505	81/male	Dependant	29-09-2021	02-10-2021	30 year	9.1	ON OHA	157	y	28	y	236	y	254	y
52	1180763	63/male	ernment emplo	27-09-2021	11-10-2021	15 year	9.2	ON OHA	177	y	18	y	228	y	231	y
53	1185910	57/female	house wife	05-09-2021	10-09-2021	NON DIABETIC	-	-	89	n	30	y	291	y	200	n
54	1189502	68/Male	Shopkeeper	11-10-2021	15-10-2021	NON DIABETIC	-	-	110	n	22	y	277	y	256	y
55	1196173	76/Female	house wife	29-10-2021	05-11-2021	10 year	10.2	ON INSULIN	172	y	41	n	291	y	297	y
56	586094	49/Male	bussiness	12-11-2021	14-11-2021	8year	9.2	ON OHA	166	y	16	y	234	y	348	y
57	854708	72/Male	Dependent	16-11-2021	17-11-2021	25years	11.1	ON INSULIN	130	n	11	y	219	y	240	y
58	1151765	54/Female	Housewife	23-11-2021	25-11-2021	NON DIABETIC	-	-	145	y	28	y	278	y	261	y
59	1256943	63/Female	Shopkeeper	29-11-2021	30-11-2021	13years	9.3	ON OHA	115	n	41	n	210	y	231	y
60	1207443	74/Female	house wife	30-11-2021	01-12-2022	15years	9.1	ON OHA	161	y	32	y	268	y	240	y
61	1021952	68/Male	bussiness	29-11-2021	05-12-2022	20years	7.8	ON OHA	159	y	28	y	298	y	200	n
62	1208335	64/Male	laywer	30-11-2021	06-12-2021	7years	8.2	ON OHA	125	n	34	y	238	y	175	n
63	1211071	77/Male	shopkeeper	01-12-2021	04-12-2021	25years	11.1	ON INSULIN	168	y	18	y	277	y	255	y
64	1214960	85/Female	house wife	02-12-2021	10-12-2021	30years	10.1	ON INSULIN	198	y	25	y	221	y	265	y
65	1213749	68/Female	Housewife	02-12-2021	05-12-2021	10years	6.9	ON OHA	98	n	38	n	231	y	191	n
66	1123926	59/Male	Shopkeeper	03-12-2021	05-12-2021	12years	7.3	ON OHA	132	y	29	y	266	y	288	y
67	1208337	65/Male	Housewife	04-12-2021	10-12-2021	15years	9.3	ON OHA	105	n	25	y	211	y	205	y
68	1212604	68/Male	bussiness	06-12-2021	11-12-2021	28years	8.6	ON OHA	136	y	40	n	197	n	212	y
69	1214396	59/female	-	10-12-2021	15-12-2021	10years	11	ON INSULIN	177	y	31	y	210	y	235	y
70	1210551	68/female	housewife	12-12-2021	17-12-2021	12years	10.1	ON OHA	157	y	29	y	201	y	240	y
71	1213766	73/Female	housewife	15-12-2021	20-12-2021	15years	9.5	ON OHA	200	y	21	y	387	y	396	y
72	78478	55/Female	housewife	16-12-2021	19-12-2021	5years	7.2	ON OHA	101	n	40	n	198	n	277	y
73	1208961	77/male	dependant	20-12-2021	26-12-2021	NON DIABETIC	-	-	96	n	25	y	131	n	145	n
74	1213891	65/Male	Shopkeeper	22-12-2021	27-12-2021	11years	7.6	ON OHA	126	n	27	y	238	y	299	y
75	1203165	71/Female	house wife	24-12-2021	27-12-2021	12years	8	ON OHA	149	y	35	n	261	y	260	y
76	902198	72/Male	shopkeeper	26-12-2021	30-12-2021	7years	9.2	ON OHA	91	n	46	n	249	y	265	y

		RISK FACTORS																
		BMI - kg/m2					waist circumfrence (cm)			Lab Parameter							HOMA - IR	
Sr. No	MRD NO	BMI (kg/m2)	normal	over weight (23-24.9)kg/m2	obese>/=25 kg/m2	weight (kg)	waist circumfrence (cm)	Men >94cm	female >80cm	Platelet count (/UL)	AST levels (U/L)	ALT levels (U/L)	AST/ALT Ratio	Metabolic syndrome	CRP (mg/L)	Ferritin (ng/ml)	absolute value	>/=2.5
39	1140441	21.3	y	-	-	72kgs	91cm	-	y	81,000	46	70	0.65	NO	6	102	1.3	n
40	1150300	26	-	-	y	78kgs	87cm	n	-	1,10,000	78	78	1	NO	4	212	1.1	n
41	914654	28	-	-	y	91kgs	97cm	-	y	74,000	50	70	0.71	yes	26	700	3.4	y
42	1150555	23.5	-	y	-	68kgs	84cm	-	y	1,25,000	56	76	0.73	NO	2	151	2.9	y
43	1161920	27.9	-	-	y	80kgs	93cm	n	-	58,000	41	78	0.52	yes	10	116	3.7	y
44	1162688	26	-	-	y	78Kgs	98cm	y	-	1,75,000	48	48	1	yes	60	1992	3.9	y
45	1160398	23.6	-	y	-	63kgs	82cm	n	-	1,10,000	56	73	0.76	NO	1	181	1.9	n
46	1161193	27.8	-	-	y	91kgs	100cm	-	y	1,10,000	71	50	1.4	Yes	41	271	4.12	y
47	1140612	26	-	-	y	89kgs	101cm	-	y	75,000	48	48	1	yes	6	342	3.1	y
48	1176027	29	-	-	y	115kgs	101cm	y	-	80,000	47	77	0.61	yes	34	482	4.7	y
49	1172979	28.2	-	-	y	96kgs	104cm	y	-	1,15,000	52	46	1.1	yes	16	172	3.92	y
50	1180763	29	-	-	y	106kgs	109cm	y	-	1,50,000	70	77	0.9	yes	17	239	4.45	y
51	853505	25.7	-	-	y	85kgs	107cm	y	-	84,000	50	50	1	yes	10	116	3.91	y
52	1180763	27.12	-	-	y	95kgs	100cm	y	-	98,000	48	58	0.82	yes	31	214	4	y
53	1185910	29	-	-	y	91kgs	103cm	-	y	75,000	44	48	0.91	yes	17	1200	2.85	y
54	1189502	26	-	-	y	92kgs	89cm	n	-	1,12,000	78	58	1.34	yes	12	414	3.7	y
55	1196173	24.1	-	y	-	70kgs	81cm	-	y	91,000	55	58	0.94	yes	1	44	3.6	y
56	586094	26.1	-	-	y	92kgs	104cm	y	-	1,00,000	49	49	1	yes	2	2121	4.2	y
57	854708	27.5	-	-	y	96kgs	107cm	y	-	1,50,000	51	57	0.89	yes	12	181	4	y
58	1151765	29.4	-	-	y	98kgs	105cm	-	y	61,000	46	50	0.92	yes	19	333	3.92	y
59	1256943	24	-	y	-	78kgs	90cm	-	y	1,10,000	71	71	1	yes	6	92	4	y
60	1207443	25.1	-	-	y	77kgs	95cm	-	y	78,000	59	49	1.2	yes	12	1511	4.3	y
61	1021952	27	-	-	y	95kgs	100cm	y	-	55,000	61	61	1	yes	18	300	4.75	y
62	1208335	24.35	-	y	-	84kgs	89cm	n	-	48,000	55	58	0.94	yes	7	258	3.67	y
63	1211071	28.7	-	-	y	94kgs	103cm	y	-	83,000	41	55	0.74	yes	21	755	4.7	y
64	1214960	27.1	-	-	y	89kgs	96cm	-	y	88,000	56	56	1	yes	4	421	2.97	y
65	1213749	25.55	-	-	y	90kgs	100cm	-	y	98,000	57	65	0.87	yes	6	152	3	y
66	1123926	26.12	-	-	y	88kgs	101cm	y	-	67,000	58	69	0.84	yes	12	321	3.22	y
67	1208337	27	-	-	y	95kgs	100cm	y	-	54,000	69	69	1	yes	27	103	4.2	y
68	1212604	26.4	-	-	y	89kgs	99cm	y	-	68,000	79	79	1	yes	6	113	3.9	y
69	1214396	27.1	-	-	y	90kgs	91cm	-	y	78,000	56	56	1	yes	2	500	3.4	y
70	1210551	28	-	-	y	85kgs	93cm	-	y	79,000	49	68	0.72	yes	28	1178	5.2	y
71	1213766	26.7	-	-	y	78kgs	95cm	-	y	1,50,000	50	60	0.83	yes	3	268	4.2	y
72	78478	25.1	-	-	y	80kgs	102cm	-	y	1,12,000	43	79	0.54	yes	23	555	4.7	y
73	1208961	27.1	-	-	y	90kgs	106cm	y	-	90,000	65	73	0.89	no	13	147	1.1	n
74	1213891	26.2	-	-	y	82kgs	96cm	y	-	89,000	80	80	1	yes	31	987	4.9	y
75	1203165	27	-	-	y	94kgs	105cm	-	y	1,12,000	71	71	1	yes	26	753	4.2	y
76	902198	23	-	y	-	80kgs	93cm	n	-	1,00,000	55	65	0.84	yes	12	587	4	y

						Diabetes mellitus			lipid profile							
Sr. No	MRD NO	AGE/ SEX	OCCUPATION	DATE OF ADMISSION	DATE OF DISCHARGE	Duration	Hba1c levels (%)	On diet /drug therapy	LDL levels (mg/dl)	Ldl levels >130mg/dl	HDL levels (mg/dl)	HDl<35 mg/dl	Total cholesterol (mg/dl)	Total cholesterol >200mg/dl	Triglycerides(mg/dl)	Triglycerides >200mg/dl
77	1057873	63/Female	house wife	27-12-2021	30-12-2021	8years	10	ON OHA	111	n	40	n	266	y	285	y
78	1246257	82/Male	Farmer	28-12-2021	01-01-2022	25years	7	ON OHA	96	n	31	y	211	y	225	y
79	1245530	53/Female	house wife	28-12-2021	31-12-2021	5years	6.7	ON OHA	150	y	21	y	277	y	199	n
80	188436	68/female	Farmer	28-12-2021	31-12-2021	12years	8.4	ON OHA	120	n	27	y	245	y	245	y
81	241078	51/Male	shopkeeper	29-12-2021	31-12-2021	NON DIABETIC	-	-	130	n	24	y	281	y	223	y
82	91564	65/female	housewife	31-12-2021	02-02-2022	15years	8.1	ON OHA	99	n	48	n	197	n	266	y
83	1239835	61/male	Shopkeeper	31-12-2021	03-01-2022	5years	6.9	ON OHA	152	y	33	y	201	y	249	y
84	856911	83/Male	Farmer	01-01-2022	05-01-2022	35years	9.6	ON OHA	133	y	35	n	256	y	216	y
85	1031365	80/Male	bussiness	01-01-2022	05-01-2022	22years	10	ON OHA	167	y	21	y	187	n	190	n
86	1240545	45/male	bussiness	02-01-2022	05-02-2022	5years	7.3	ON OHA	160	y	25	y	222	y	254	y
87	1109415	68/male	shopkeeper	01-01-2022	06-01-2022	11years	10.1	ON OHA	93	n	30	y	211	y	355	y
88	1235566	71/female	house wife	02-01-2022	06-01-2022	21years	7.7	ON OHA	87	n	30	y	226	y	205	y
89	1241178	45/male	Farmer	03-01-2022	07-01-2022	NON DIABETIC	-	-	71	n	40	n	102	n	106	n
90	1240885	77/female	housewife	05-01-2022	10-01-2022	20years	8.9	ON OHA	103	n	25	y	216	y	247	y

		RISK FACTORS																
		BMI - kg/m2					waist circumfrence (cm)			Lab Parameter							HOMA - IR	
Sr. No	MRD NO	BMI (kg/m2)	normal	over weight (23-24.9)kg/m2	obese>/=25 kg/m2	weight (kg)	waist circumfrence (cm)	Men >94cm	female >80cm	Platelet count (/UL)	AST levels (U/L)	ALT levels (U/L)	AST/ALT Ratio	Metabolic syndrome	CRP (mg/L)	Ferritin (ng/ml)	absolute value	>/=2.5
77	1057873	26.1	-	-	y	83kgs	99cm	-	y	55,000	41	76	0.53	yes	6	248	2.9	y
78	1246257	28.6	-	-	y	101kgs	103cm	y	-	81,000	56	68	0.82	yes	34	359	5.1	y
79	1245530	30	-	-	y	112kgs	109cm	-	y	96,000	71	78	0.91	yes	27	624	5	y
80	188436	25.7	-	-	y	96kgs	100cm	-	y	25,000	68	68	1	yes	45	759	4.2	y
81	241078	27	-	-	y	99kgs	107cm	y	-	1,00,000	43	59	0.72	yes	31	574	4.7	y
82	91564	29.5	-	-	y	103kgs	106cm	-	y	75,000	53	53	1	yes	30	965	5.1	y
83	1239835	26.1	-	-	y	100kgs	106cm	y	-	63,000	65	65	1	yes	16	87	3.3	y
84	856911	27.6	-	-	y	97kgs	101cm	y	-	1,20,000	52	59	0.88	yes	14	456	3	y
85	1031365	29	-	-	y	115kgs	110cm	y	-	96,000	58	58	1	yes	21	125	4.7	y
86	1240545	28.4	-	-	y	89kgs	95cm	y	-	55,000	63	67	0.94	yes	29	221	4.1	y
87	1109415	29.4	-	-	y	96kgs	101cm	y	-	1,05,000	45	45	1	yes	14	125	4.5	y
88	1235566	29	-	-	y	101kgs	107cm	-	y	57,000	49	50	0.98	yes	53	493	3.9	y
89	1241178	22.1	y	-	-	75kgs	80cm	n	-	1,35,000	80	80	1	NO	5	191	1.1	n
90	1240885	26.7	-	-	y	89kgs	98cm	-	y	69,000	67	77	0.87	yes	13	578	3.7	y

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Date 05/01/22

The Principal,
DMC, Ludhiana.

Subject: **Approval of Plan of Thesis.**

This is to inform you that the Faculty of Medical Sciences in its meeting held on 29.10.2021 has approved the plan of thesis of **Gautam Bedi**, a student of your college for **MD General Medicine** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis

Study of risk factors in patient with advanced fibrosis in non alcoholic fatty liver disease with mild elevation of transaminases.

Supervisor
Dr. Dinesh Gupta
Prof. & Head,
Dept. of Medicine,
DMCH, Ludhiana.

Co-Supervisor

Dr. Varun Mehta
Prof.,
Dept. of Gastroenterology,
DMCH, Ludhiana.

The student has to submit the four copies of thesis (along with PDF format) , to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

S P Singh

Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

47. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*
48. *The student may submit the thesis as per the schedule already conveyed i.e. for May June examination 30th Nov of the preceding the year of examination and for Nov/Dec examinations 31st May of the year of examination*

STUDY OF RISK FACTORS IN PATIENT WITH ADVANCED FIBROSIS IN NON ALCOHOLIC FATTY LIVER DISEASE WITH MILD ELEVATION OF TRANSAMINASES

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

MD

MEDICINE

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES

FARIDKOT

MARCH 2021

DR GAUTAM BEDI

DEPARTMENT OF MEDICINE

DAYANAND MEDICAL COLLEGE AND HOSPITAL

LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	STUDY OF RISK FACTORS IN PATIENT WITH ADVANCED FIBROSIS IN NON ALCOHOLIC FATTY LIVER DISEASE WITH MILD ELEVATION OF TRANSAMINASES
For the degree of	MEDICINE
Name of the candidate	Dr Gautam Bedi
Supervisor	Dr. Dinesh Gupta, Professor & Head, Department of Medicine, DMC&H Ludhiana
Co-supervisor	Dr Varun Mehta, Professor, Department of Gastroenterology, DMC&H Ludhiana
Institution	Dayanand Medical College & Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction: Non alcoholic fatty liver (NAFLD) is a global health problem. A significant number of patient with NAFLD have normal aminotransferase levels. Several studies have consistently shown that when patients with normal aminotransferase level underwent transient elastography significant level of fibrosis were commonly observed and not significantly different than those in NAFLD patient with elevated aminotransferase level. Various risk factors are known for this disease and each of them have different prevalence.

Aim of Study: To analyse the risk factors in patient with non alcoholic fatty liver disease with advanced fibrosis, who have mild elevation of transaminases.

Materials & methods:

STUDY DESIGN: - Prospective Observational study

SETTING: - O.P.D and I.P.D patients in Medicine department and Gastroenterology department in tertiary care hospital

Clinical Significanco:

The most important predictor of adverse outcomes in NAFLD is fibrosis causing significant mortality and morbidity. This study will analyze the risk factors causing advanced fibrosis in patients with NAFLD with mild elevation of transaminases.

KEYWORDS: Nafld, Fibrosis, Ast, Alt, Obesity, Metabolic syndrome, Diabetes Mellitus, Transient Elastography.

(Signature)	(Signature)	(Signature)	(Signature)
Candidate	Co-supervisor	Supervisor	Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"STUDY OF RISK FACTORS IN PATIENT WITH ADVANCED FIBROSIS IN NON ALCOHOLIC FATTY LIVER DISEASE WITH MILD ELEVATION OF TRANSAMINASES"** exist in the Department of General Surgery, DMC&H, Ludhiana and will be provided to be candidate. We will see that the data being included in the thesis are genuine and is collected by the candidate himself under our supervision and guidance.

Supervisor

Dr Dinesh Gupta
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Co-Supervisor

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HEAD OF DEPARTMENT

Dr. Dinesh Gupta
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Place: _____

Date: _____

APPROVAL PROFORMA
BY RESEARCH & ETHICAL COMMITTEE
DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA

Name of candidate	Dr. Gautam Bedi
Department	Medicine
Topic of Thesis	STUDY OF RISK FACTORS IN PATIENT WITH ADVANCED FIBROSIS IN NON ALCOHOLIC FATTY LIVER DISEASE WITH MILD ELEVATION OF TRANSAMINASES
Likely date of appearing in PG examination	MAY 2023
Date of enrollment	25th July 2020
Name of Head of Department	Dr. Dinesh Gupta
1) Supervisor **2) Co-Supervisor**	Dr. Dinesh Gupta Dr. Varun Mehta
Signature of Members of Research Committee with Stamp	**Signature of Members of Ethics Committee with Stamp**
Dr. Harpreet Kaur (Professor & Head, Pathology)	Mr. R K Sharma (Legal Expert)
Dr. Jaspal Singh (Professor & Head, Surgery)	Dr. Ramit Mahajan (Associate Professor, Gastroenterology)
Dr. Dinesh Gupta (Professor & Head, Medicine)	Dr. Anu Sharma (Professor, Anatomy)
Dr. Sandeep Kaushal (Dean Academics & Professor & Head, Pharmacology)	Dr. Sandeep Kaushal (Dean Academics & Professor & Head, Pharmacology)
Dr. Gurpreet S Wander (Vice Principal)	Dr. Gurpreet S Wander (Vice Principal & Professor & Head, Cardiology)
	Dr. Gagandeep Singh (Secretary, Ethics Committee Professor & Head, Neurology)

Approved: Yes / No

Dr. Sandeep Puri
Chairperson
Research Committee

Approved: Yes / ~~No~~

Prof. Arvind Malhotra
Chairperson
Ethics Committee

BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT

PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

1	NAME OF THE CANDIDATE AND ADDRESS	DR. GAUTAM BEDI 4101, Durga Puri, Haibowal kalan, Ludhiana
2	NAME OF THE INSTITUTE	DMCH, LUDHIANA
3	COURSE OF STUDY AND SUBJECT	MEDICINE
4	DATE OF ADMISSION OF COURSE	25th, JULY,2020
5	TITLE OF THE TOPIC	STUDY OF RISK FACTORS IN PATIENT WITH ADVANCED FIBROSIS IN NON ALCOHOLIC FATTY LIVER DISEASE WITH MILD ELEVATION OF TRANSAMINASES

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Non-alcoholic fatty liver disease (NAFLD) has become the most common cause of chronic liver disease among adults [1]. NAFLD includes a spectrum of diseases ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) to advanced fibrosis and cirrhosis and hepatocellular carcinoma, causing considerable liver-related morbidity and mortality[2,3]. Advanced Fibrosis is defined as stage F3-F4 on transient elastography. There is increasing attention for the clinical association among NAFLD and its various risk factors. Prevalence of the disease is estimated to be around 9-32% in the general Indian populations, with higher incidence among peoples associated with various risk factors [4]. Various risk factors can be categorized into Demographics, Anthropometric, Comorbidities, Laboratory parameters. Demographic parameters include age(in years), sex. Anthropometrics includes BMI, weight. Comorbidities includes Type 2 diabetes mellitus, hypertension, dyslipidemia, hypothyroidism, metabolic syndrome.

Laboratory measures include Platelet count, Transaminases including (AST, ALT), Hba1c, Total cholesterol, Triglycerides, HDL – cholesterol and LDL – cholesterol [5,6]. It has been seen that patients detected fatty liver incidentally on USG when underwent transient elastography were found to have advance fibrosis, though their AST and ALT levels were within normal limit. The growing prevalence of NAFLD is attributed to global increases in the prevalence of metabolic risk factors like T2DM, impaired glucose tolerance, dyslipidemia and central obesity. Obesity has been one of the major risk factor of NAFLD and severity of fibrosis is seen more in obese people developing NAFLD than lean people developing NAFLD [7]. Various lab parameters like platelet count, ast/alt ratio, Hba1c, total cholesterol, triglycerides, HDL cholesterol and LDL cholesterol if identified early and appropriate steps taken can help us to decrease the progression of the disease .study would help us see each risk factor and its delineament from the normal value and their association with NAFLD and severity of fibrosis. Hypertension

Dyslipidemia, Metabolic syndrome and Hypothyroidism are the other risk factors which have been linked to NAFLD. This study will also identify whether if these parametric values are related to the degree of fibrosis or not. The pathogenesis of NAFLD is not completely elucidated but insulin resistance and oxidative stress appear to play a major role. Obesity, Type 2 Diabetes mellitus, Dyslipidemia, Metabolic syndrome all result in insulin resistance and increase oxidative stress which results in development and progression of NAFLD. NAFLD with advanced fibrosis can even present with only mild elevation of transaminases. Mild elevation of transaminases is defined as elevation less than 5 times the upper limit of normal value[9].

6.2 REVIEW OF LITERATURE

Pelusi S, et al. Prevalence and Risk Factors of Significant Fibrosis in Patients With Nonalcoholic Fatty Liver Without Steato hepatitis. They aimed to estimate the prevalence of fibrosis in patients without NASH and risk factors for fibrosis. They analysed data from 1738 subjects (44.9% with severe obesity) in a cross-sectional liver biopsy cohort enrolled at referral centres in Italy and Finland. Biopsy specimens were analysed histologically by a blinded pathologist at each centre, and a diagnosis of NASH was made based on steatosis (≥5% of hepatocytes), hepatocellular ballooning, and lobular inflammation. They also collected data on demographic features, metabolic comorbidities, and genetic factors, and performed logistic regression analyses. Findings were validated using data from 118 consecutive patients with NAFLD who underwent sequential liver biopsies at tertiary referral centres in Italy. It was concluded that in an analysis of biopsy specimens collected from patients with NAFLD at a single time point, one third of patients with significant fibrosis did not have NASH. They validated this finding in a separate cohort. In patients without NASH, fasting hyperglycemia, severe steatosis, mild inflammation or ballooning, and the PNPLA3 I148M variant identified those at risk of significant fibrosis.[10,11]

Samer Gawrieh, et al. Histologic findings of advanced fibrosis and cirrhosis in patients with NAFLD who have normal aminotransferase levels. They conducted a study to characterize the prevalence of and factors associated with advanced liver histology in patients with histologically characterized NAFLD and normal aminotransferase levels. They evaluated 534 adults with biopsy-proven NAFLD and ALT and AST < 40 U/L within 3 months of their liver biopsy. Histological phenotypes of primary interest were NASH with stage 2-3 fibrosis (NASH F2-3) and cirrhosis. Using multiple logistic regression models with Akaike's Information Criteria (AIC), they identified variables associated with these histological phenotypes. They developed and internally validated their clinical prediction models. The prevalence of NASH F2-F3 and cirrhosis were 19% and 7%, respectively. The best

multiple regression AIC model for NASH F2-3 consisted of type 2 diabetes, White race, lower LDL, lower platelet count, higher AST/ALT ratio, higher serum triglycerides, and hypertension. The best AIC model for cirrhosis consisted of lower platelet count, lower AST/ALT ratio, higher BMI, and female sex. The area under the receiver operator curves of the prediction models were 0.70 (95% CI: 0.65-0.76) for detecting NASH-F2-3 and 0.85 (95% CI: 0.77-0.92) for detecting cirrhosis. When models were fixed at maximum Youden's index, their positive and negative predictive values were 35% and 88% for NASH F2-F3 and 30% and 98% for cirrhosis, respectively: Clinically significant histological phenotypes were observed in patients with NAFLD and normal aminotransferase levels. Their models could assist the clinicians in excluding advanced liver histology in NAFLD patients with normal aminotransferase levels.[12-14]

Mishra, S., Yadav, D., Gupta, M. et al. Hyperinsulinemia predisposes to NAFLD. Metabolic syndrome contributes to pathogenesis of Type-2 diabetes and CAD. Insulin Resistance is the key factor of metabolic syndrome implicated in development of Non Alcoholic Fatty Liver Disease (NAFLD). In present study they have investigated the prevalence of NAFLD in metabolic syndrome and contribution of metabolic risk factors in causation of NAFLD in non-diabetic North Indian male population. They studied 495 non-diabetic, nonalcoholic subjects (age 30–65 years). Metabolic Syndrome was assessed by using ATP III and ADA (2005) criteria. Anthropometric factors-Waist circumference and blood pressure were measured. Fasting serum samples were analyzed for Glucose, Triglycerides, Cholesterol and its fractions, Insulin, Alanine transaminase, Aspartate transaminase, Gamma glutamyl transferase and free fatty acids. Insulin resistance was estimated by Homeostasis Model and Insulin sensitivity by QUICKI Index. Liver ultrasonographic scanning was used for assessing fatty liver. The prevalence of metabolic syndrome and NAFLD was 24% and 14.8% respectively in non-alcoholic population and 27% of metabolic syndrome had NAFLD which was associated with hyperinsulinemia, insulin resistance, insulin insensitivity along with elevated levels of

waist circumference, blood pressure, triglyceride, FFA and decreased HDL-Cholesterol. The prevalence of NAFLD increased with insulin resistance and clustering of metabolic risk factors.[15]

Donati G, et al. Increased prevalence of fatty liver in arterial hypertensive patients with normal liver enzymes: role of insulin resistance. Gut 2004; 53: 1020–1023. The aim of the study was to test the hypothesis that fatty liver with normal liver enzymes occurs more frequently in arterial hypertensive patients and to establish whether this condition is associated with insulin resistance. Plasma metabolic parameters, body mass index, and the presence of fatty liver were investigated. Insulin resistance was estimated from plasma insulin and glucose as the homeostasis model assessment index. Stepwise logistic regression and multivariate regression analysis were used on the combined sample to identify variables independently associated with fatty liver and insulin resistance. Hypertensive patients had a significantly higher prevalence of fatty liver, higher insulin resistance, and slightly higher body mass index than controls. Multivariate logistic regression identified insulin resistance and body mass index as factors independently associated with fatty liver. Multivariate regression analysis showed insulin resistance to be predicted by alanine transaminase , presence of arterial hypertension and body mass index .in the end they concluded that higher prevalence of non-alcoholic fatty liver in non-obese hypertensive patients with normal liver enzymes appears to be related to increases in insulin resistance and body weight.[16,17]

Gupte P, Amarapurkar D, et al. Non-alcoholic steatohepatitis in type 2 diabetes mellitus. Non-alcoholic steatohepatitis (NASH) is commonly associated with type 2 diabetes mellitus (DM). Prevalence of NASH in type 2 DM has not been well studied and there is an epidemic rise in type 2 DM in Asian and Western populations. Its association with chronic liver disease in the form of NASH makes it an important health problem. Hence they have studied its prevalence and correlation of biochemical parameters with histological grades of non-alcoholic fatty liver disease (NAFLD) in otherwise asymptomatic type 2 DM patients.In

their study one hundred and forty-eight individuals were screened. Forty-eight individuals were excluded due to history of alcohol intake or liver disease as a result of other causes. One hundred non-alcoholic individuals with type 2 DM underwent abdominal ultrasonography (US abdomen). Forty-nine patients had evidence of fatty liver on US abdomen, and 32 of these 49 patients underwent liver biopsy. Results were four of 32 (12.5%) individuals had steatosis alone. Mild, moderate and severe NASH was present in 21/32 (65.5%), 4/32 (12.5%) and 3/32 (9.35%), respectively. Fibrosis was present in 7/32 (21.8%) patients (four grade 1 and three grade 3). There was no significant difference in body mass index (BMI), transaminase levels, serum cholesterol and triglyceride levels among patients with non-alcoholic fatty liver disease. They concluded that the prevalence of NASH is high in type 2 DM patients and liver biopsy is the only investigation to differentiate between non-alcoholic fatty liver and steatohepatitis.[18,19]

Assy N, Kaita K, et al. Fatty infiltration of liver in hyperlipidemic patients. Hyperlipidemia is a known risk factor for fatty infiltration of the liver, a condition that can progress to cirrhosis and liver failure. The objectives of their study were to document the prevalence of fatty infiltration in the livers of hyperlipidemic patients and to identify the predictor variables associated with this condition. Over an 18-month recruitment period, clinical, biochemical, and radiologic assessments were performed in a cross-sectional manner in 95 adult patients referred to an urban hospital-based lipid clinic for evaluation and management of hyperlipidemia. The mean (+/-SD) age of the patients was 55 +/- 13 years. Forty-eight (51%) were male. Fifty-two patients (55%) had hypercholesterolemia, 25 (26%) severe hypertriglyceridemia, 14 (15%) mixed hyperlipidemia, and 4 (4%) moderate hypertriglyceridemia. Obesity and diabetes were present in 36 (38%) and 12 (12%) of cases, respectively. A total of 61 (64%) patients had elevated liver enzyme tests. The most common enzyme abnormalities were an elevated serum ALT in 45 (47%) and GGT in 43 (45%) of patients. Ultrasound findings revealed diffuse fatty liver in 47 patients (50%), of which 21 cases (22%) were mild, 18 (19%)

moderate, and 8 (9%) severe. The majority of patients with hypercholesterolemia [35/52 (67%)] had normal ultrasounds, whereas severe hypertriglyceridemia and mixed hyperlipidemia were frequently associated with radiologic evidence of fatty liver. Independent predictors of fatty liver were; AST, hyperglycemia and age. In a model incorporating known risk factors for fatty liver, diabetes was the only risk factor other than hypertriglyceridemia that was significantly associated with fatty infiltration. No such effect was seen with age, gender, obesity, or alcohol consumption. In conclusions, the results of their study indicated that ultrasonographic evidence of fatty infiltration of the liver was evident in approximately 50% of patients with hyperlipidemia. Hypertriglyceridemia is the lipid profile most often associated with this condition. Serum AST values, hyperglycemia, and age independently predict the presence of fatty infiltration, while hypertriglyceridemia and diabetes are the only risk factors that significantly increase the risk of fatty infiltration in hyperlipidemic patients [20-22].

6.3 AIMS AND OBJECTIVES OF THE STUDY

1. To analyse the risk factors in patient with non alcoholic fatty liver disease with advanced fibrosis, who have mild elevation of transaminases.

7.0 MATERIALS AND METHODS

STUDY SITE- The study would be carried out in Department and O.P.D. of Medicine and Gastroenterology, Dayanand Medical College and Hospital Ludhiana

STUDY TYPE – Prospective Observational Study.

7.1 SOURCE OF DATA

All the patients in O.P.D and in department of medicine and gastroenterology with NAFLD, with advanced fibrosis on transient elastography and having mildly elevated transaminases.

7.2 METHOD OF COLLECTION OF DATA

Inclusion Criterion:

- Age >18 years
- Non Alcoholics
- Advance fibrosis on transient elastography
- Mildly Elevated Transaminases levels (upto 5 times of upper limit of normal)
- Patient who give the consent for the study

Exclusion Criterion:

- Patient who don't give the consent for the study
- Age<18 years
- Alcoholic liver disease
- Fibrosis due to viral liver disease
- Haemochromatosis , wilsons disease
- PBC , PSC, Autoimmune hepatitis

Non-alcoholic fatty liver disease (NAFLD) is defined by macrovesicular steatosis in ≥5% hepatocytes, in the absence of a secondary cause such as alcohol or drugs. It encompasses a spectrum of disease from non-alcoholic fatty liver (NAFL) through to non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis.

The patients who will be diagnosed with NAFLD and will have advanced fibrosis on transient elastography will be included in the study after the informed consent of the individual.

A prospective observational study will be carried on all the patients.

Information from the patients will be collected through a pre designed Performa for each patient being enrolled in the study.

Laboratory parameters will be collected from patients medical records.

Proper history, anthropometric data, will be collected from the patients.

Root cause analysis will be done.

Duration of Study / Number of Cases: 12 months

Outcome:

Analysis of risk factor of NAFLD with advanced fibrosis with mild elevation of transaminases.

Statistical Analysis:

Prospective Observational study will be carried out on OPD and IPD patients of NAFLD in Medicine and Gastroenterology department, from March 2021 to February, 2022.

Data will be described in terms of range, mean +/- Standard Deviation (+/- SD), median, frequencies, (number of cases) and relative frequencies (percentages) as appropriate. All statistical calculations will be done using (statistical package for social science) SPSS 21 Version (SPSS Inc., Chicago, IL, USA) statistical programme for Microsoft Windows.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

No.

7.4 HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Yes

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PROFORMA

Sr. No

NAME MRD NO.

AGE/ SEX:

FATHER'S NAME

ADDRESS

OCCUPATION:

DATE OF ADMISSION

DATE OF DISCHARGE

RISK FACTORS –

1 Diabetes mellitus

a)Duration

b)Hba1c levels

c)On diet /drug therapy

2 lipid profile

a)LDL levels

b)HDL levels

c)Total cholesterol

d)Triglycerides

3 Anthropometric

a)BMI

b)weight

c)waist

Signature of Candidate

Signature of Supervisor

4 Lab Parameter

a) Platelet count

b) AST levels

c) ALT levels

d) AST/ALT Ratio

5 Metabolic syndrome

Yes / No

6 CRP

7 Ferritin

8 HOMA - IR

Signature of Candidate

Signature of Supervisor

INFORMED PATIENT CONSENT

Date: _____

I.....D/o, W/o, S/o.....
.....am willing to participate in the study. I am ready to participate in this study on my own **"STUDY OF RISK FACTORS IN PATIENT WITH ADVANCED FIBROSIS IN NON ALCOHOLIC FATTY LIVER DISEASE WITH MILD ELEVATION OF TRANSAMINASES"** I affirm that I have not been given any financial incentive and no pressure has been put on me to give the consent. The purpose of this research has been explained to me and I believe that it is for the benefit of science and mankind. I have been explained about the risk in this research and I understand that the risk is very minimal. I have been explained the method of participating in this research work.

I can choose to opt out of this research at any time and my opting out will not have any effect on my treatment.

.....
Signature of the Witness

Name:

.....
Signature of the patient

Signature of Candidate

Signature of Supervisor

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य "STUDY OF RISK FACTORS IN PATIENT WITH ADVANCED FIBROSIS IN NON ALCOHOLIC FATTY LIVER DISEASE WITH MILD ELEVATION OF TRANSAMINASES" में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____

गवाह के हस्ताक्षर

नाम:

_____

रोगी के हस्ताक्षर/अंगूठे का निशान

नाम:

_____

अन्वेषक के हस्ताक्षर

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁਤਰ/ਪੁਤਰੀ_____

ਵਾਸੀ _____

"STUDY OF RISK FACTORS IN PATIENT WITH ADVANCED FIBROSIS IN NON ALCOHOLIC FATTY LIVER DISEASE WITH MILD ELEVATION OF TRANSAMINASES" ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

_____ _____

ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____ ਮਿਤੀ_____

ਪਤਾ _____ ਪਤਾ _____

_____

ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

_____

ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ